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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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## 1983

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# INTRODUCTION

The activities of the Agency are directed primarily to research on the causes of cancer, with the aim of generating and disseminating information useful for the prevention of human cancer. The coupling of field and bench activities, both intra- and extra-mural, has allowed the Agency to develop programmes that represent an integrated approach to the identification, on the one hand, of causative factors in human cancer and, on the other, of individuals and population groups at different risks of developing cancer. The Agency has recently devoted part of its activities to research more specifically related to the primary prevention of cancer through intervention, and to the evaluation of early detection and mass screening programmes for cancer control and secondary prevention.

A brief outline of the main projects of the Agency is given below. The work of the Agency is described in detail in the *Report* itself, and a detailed table of contents and an index have been included to facilitate reading of the *Report*.

*Geographical Distribution and Time Trends*

Because certain necessarily strict criteria for accuracy and completeness of information are respected, data on cancer incidences have until recently been collected mainly from industrialized countries. The outcome of this activity has been the publication *Cancer Incidence in Five Continents*, of which the fourth volume appeared in October 1982. This volume comprises data from 79 registries in 32 countries and is considered a unique international resource, essential for basic environmental studies of the etiology of cancer.

There are, however, large areas of the world for which no incidence data are available. Recently, therefore, the Agency has given special attention to the collection of high quality data from developing countries. The provision of statistical material on geographical, ethnic and temporal variations in cancer occurrence is critical to a realistic evaluation of the magnitude of the cancer problem, to the formulation of etiological hypotheses, and to the setting of priorities for intervention. The Agency is at present collecting information from about 55 countries in Asia, Africa and South America. A simple cancer registration system suitable for use on a microcomputer has been developed at the Agency which is designed specifically for use by registries in developing countries and which will incorporate facilities for rapid retrieval and simple analysis of data. Collaborating in a cancer control programme in Sudan, supported by the Cancer Unit, WHO/HQ, and EMRO, the Agency is providing assistance for the improvement of cancer registration procedures.

Fig. A. New members of the Scientific Council
1983-1986

Professor H. J. Evans

Dr B. Henderson

Dr R. Kroes

An estimate has been made of the current world cancer burden for the 24 geographical regions of the United Nations. The most common cancers occurred in the following order:

| | *Males* | *Females* | *Combined males and females* |
|---|---|---|---|
| 1. | Lung | Breast | Stomach |
| 2. | Stomach | Cervix uteri | Lung |
| 3. | Large bowel | Stomach | |
| 4. | Mouth/Pharynx | Large bowel | |
| 5. | Prostate | Lung | |

It is interesting to note that, globally, for the two sexes combined, stomach cancer still ranks first on a world-wide basis and lung cancer second, and that in absolute terms the most frequent malignant tumour is breast cancer in females.

*Occupational Cancer*

Man-made mineral fibres, in particular glass wool and rock wool, are used increasingly as reinforcement for plastics and, more importantly, for thermal and acoustic insulation, where they represent the substitute for asbestos. It was therefore considered important to determine whether these fibres, which have been shown to produce tumours when instilled into the pleural cavity of experimental animals, cause cancer in humans. A historical cohort study of the health risks associated with exposure to mineral fibres was therefore initiated in 1980 in 13 production facilities distributed in nine European countries. Extension of the investigation to an international level was necessary in order to increase the size of the population studied and hence the chance of detecting an effect. Analysis of the data available up to now has shown that there is no excess of mortality from all causes in the exposed workers; however, by pooling data from all factories producing glass wool, rock wool or continuous filament, lung cancer risks appear to be slightly increased 30 years after first employment, with a standard mortality ratio of 192. It is hoped that the collaboration with the industries concerned, which made the historical study possible, will continue for the five-year extension of the follow-up of workers and for an assessment of past environmental conditions. Only after these additional investigations have been completed will sufficient information be available to allow a correct interpretation of the present finding.

Other international collaborative studies on occupational cancer presently under consideration are one on silicosis and lung cancer, and one on people exposed to dioxin-contaminated substances.

*SEARCH*

The programme of international collaboration in observational studies, originally known under the acronym SEARCH (Surveillance of Environmental Aspects Related to Cancer in Humans), has as its goal the acquisition of data on possible causal relations between common cancers and relatively common human exposures through observational studies in disparate populations. Work is carried out principally by a network of collaborating investigators, who meet on a semiannual basis to coordinate protocols and to discuss common scientific and logistical

problems. The programme began formal operation in February 1983 with a case-control study of cancer of the pancreas, which will place special emphasis on the role of known stimulators of cholecystokinin release. At present, there are four collaborating centres—in Adelaide, Toronto, Utrecht and Warsaw. Active negotiations are underway with four further centres, in order to achieve a more diverse mix of populations for study.

In related projects, the SEARCH programme is involved in the development of a centre for the conduct of observational studies in Singapore, where ethnic diversity and rapid economic growth have given rise to a 'population laboratory' well suited to the testing of epidemiological hypotheses, and a potentially valuable node in the research network. SEARCH is also sponsoring methodological work on the analysis of occupational histories in case-control studies, so that this crucial aspect of the human environment may be examined effectively in specific SEARCH studies.

The format of cooperative development of protocols and frequent consultations among principal investigators means that SEARCH can be used as a vehicle for the development of epidemiological experience and expertise in areas in which it is currently lacking. Thus, SEARCH serves an educational as well as a scientific function. While extensive local epidemiological experience is not a prerequisite for a SEARCH centre, it is essential that local cases can be ascertained, random members of the general population be identified and interviewed, and that local funding be available; these criteria may effectively keep many regions of great epidemiological interest out of the SEARCH network. We hope to reduce the impact of this imbalance, which favours participation by centres in wealthy countries, by bringing into the SEARCH system centres in rapidly developing countries where aspects of the historical fact of poverty may still play an important role in determining cancer incidence.

### *Nutrition and Cancer*

The Agency is developing a major programme on the role of dietary factors in the origin of human cancer. A number of studies are in progress: these include a case-control study of adenomatous polyps of the large-bowel and investigations on the role of diet in the etiology of large-bowel cancer in Belgium, as part of a large investigation on the effects of diet on health, and in Greece where an increase in risk was associated with high meat consumption and a protective effect of green vegetables was observed.

A large prospective study on diet and the development of cancer at selected sites has been planned in Malmö, Sweden; and this is undergoing a careful final evaluation by Swedish and Agency scientists. The objectives of this study, which will involve 50 000 residents between the ages of 50 and 74 to be followed up for up to 15 years, are to investigate which, if any, particular aspects of the diet and of blood, faecal and urine biochemistry of apparently healthy people make them likely to develop cancer or some particular type of cancer. Pilot studies will be initiated in 1984.

### *Collection of Human Biological Material*

As became apparent to the planning of the prospective study in Malmö, as well as in a variety of other studies, the availability of human biological specimens represents an essential component

in the conduct of epidemiological studies. Collection of material in conjunction with specific epidemiological surveys will permit precise comparisons at individual and group levels, by using biochemical measures that are presently available or are in the process of being developed. The Agency is carrying out a world-wide survey of existing collections of biological material. A total of 570 replies have been received, of which 230 contained positive information. The latter are being analysed with a view to the possibility of utilizing some of the existing collections for specific epidemiological projects.

The Agency has initiated and maintained in its laboratory a considerable number of Burkitt's lymphoma cell lines, which have for years been supplied upon request to many laboratories around the world interested in studies of the genotype and phenotype of such cells.

*Intervention Studies on Primary Prevention*

The Singapore Government has approved a programme for the control of hepatitis B virus aimed at reducing the incidence of acute and chronic liver disease by vaccination of the following high-risk groups: children born to hepatitis B surface antigen-positive mothers, hospital personnel and contacts of hepatitis B surface antigen-positive individuals. This programme, in which the Agency collaborates with the University of Singapore, is expected to start in 1984. In order to measure the impact of this vaccination programme on liver cancer incidence, an unvaccinated control group must be available. The Government of Singapore has agreed to the use of a historical control group, which will be composed of 35 000 live births occurring during the year prior to the beginning of vaccination.

The Agency was invited by the Gambian Government and the Medical Research Council in the Gambia to consider the feasibility of a controlled trial to verify if prevention of chronic liver disease through vaccination against hepatitis B virus would also result in prevention of primary liver cancer. This project was discussed at the Agency with knowledgeable consultants, and encouragement was given to the development of an appropriate design and proposal. Subsequently, two meetings at WHO Headquarters, organized by the Cancer Unit and by the Division of Communicable Diseases, respectively, gave additional endorsement to the type of large-scale intervention programme that was envisioned. A series of ad-hoc meetings and discussions between Agency staff, appropriate staff at Headquarters and international experts on hepatitis B virus have since taken place, and there is general agreement that a large-scale intervention trial is needed and that, in Africa, the Gambia offers the optimal conditions for the successful implementation of this type of study. Since the conduct of this proposal will involve a substantial financial commitment, a number of sources of support are being considered.

Results obtained in areas with high incidences of oesophageal cancer—namely, northern Iran and certain counties in the People's Republic of China—provide strong support for the hypothesis that the natural history of the disease starts with an oesophagitis, which may progress to atrophy and dysplasia and finally to cancer. On the basis of recent surveys indicating that these precursor lesions may be related to deficiencies in riboflavin, zinc and possible vitamin A, an intervention study is being mounted to verify whether the combined administration of these substances as a dietary supplement can reduce the frequency of the precursor conditions. A similar intervention study is planned in Uzbekistan (USSR), in conjunction with a screening programme for precursor lesions of oral and oesophageal cancer.

*Endogenous Formation of Carcinogens*

A simple, sensitive method for estimating in-vivo formation of *N*-nitroso compounds was developed recently in the Agency laboratories. Initial results of an investigation carried out in China would indicate that subjects living in high-incidence areas are exposed to larger amounts of nitrate and *N*-nitroso compounds than those living in low-incidence areas. The same method—for estimating quantitatively endogenous formation of *N*-nitroso compounds—is presently being employed in several studies involving human subjects with precancerous lesions of the oesophagus and the stomach, or with conditions that create an increased risk of gastric cancer, and in asymptomatic subjects from high- and low-risk areas for cancer of the oesophagus and stomach. Three additional *N*-nitroso compounds have been identified recently in human urine samples, namely *N*-nitrosothiazolidine 4-carboxylic acid and two isomers of *N*-nitroso-2-methylthiazolidine 4-carboxylic acid. Measurement of these *N*-nitroamino acids in urine samples may make it possible to monitor exposure of human subjects to precursors like aldehyde(s) and nitrate/nitrite.

*Evaluation of Carcinogenic Risks*

The Agency continues its project on the evaluation of the carcinogenic risk of chemicals to humans, which is centred on the production of monographs now regarded as the standard source of information on environmental carcinogens by scientists, as well as by governments and regulatory agencies. The objective of this project is to identify, on the basis of all published epidemiological, experimental and other data relevant to carcinogenicity and human exposure, those chemicals, groups of chemicals and exposures to complex mixtures that may pose a carcinogenic risk to humans. Over 600 chemicals, groups of chemicals and mixed exposures were evaluated in the first 30 volumes published. Among these, seven industrial processes and occupational exposures and 23 chemicals were identified as being causally associated with human cancer, while 61 additional chemicals, groups of chemicals and industrial processes were evaluated as being probably carcinogenic to humans. The Agency is planning to devote two of the future volumes of this series to the evaluation of carcinogenic risks related to widespread cultural habits, namely, betel nut chewing and tobacco smoking.

The Agency has also developed a project to provide information on selected methods of analysis for carcinogens in the environment. This programme has resulted in the publication of a series of manuals, six of which have appeared in press. The last three volumes were devoted to aromatic amines and azo dyes, mycotoxins and *N*-nitroso compounds. In parallel, a project has been developed for the evaluation of methods for the destruction of carcinogenic wastes from laboratories; and a series of monographs is published outlining recommended methods.

*Studies on Secondary Prevention*

The Agency is carrying out a project to evaluate programmes for the early detection of cancer of the cervix. The purpose of this project is threefold: First, to generate epidemiological data on the basis of which projections given by different screening policies can be estimated. The data come from western Europe and Canada; extrapolation of the results to other areas, with perhaps much higher incidences, is done on the assumption that the natural history of the disease is the same.

Second, to develop epidemiological methods by which such data can be generated for use in areas where differences in natural history might be expected. Third, to develop methods for estimating ongoing screening programmes in terms of their effect on mortality and morbidity, particularly in regions where evaluation of trends in these rates might not be meaningful. These results will contribute to the development of effective and economic screening policies in less developed countries.

Another project is devoted to the evaluation of possible long-term hazards of both radiation and chemotherapy, from which the degree of risk for a second primary cancer has been shown on occasion to be high. This project is aimed at permitting a better assessment of the long-term hazards of different treatments while assessing the initial therapeutic benefits. The development of a necessary body of information on both radiation and chemotherapy will also enable less developed countries to protect themselves against some of the dangers of advanced technology.

*Carcinogenicity Tests*

The Agency has developed a network of national laboratories which collaborate in the long-term carcinogenicity testing of chemicals. The various components of this project (selection of chemicals and of laboratories, development of guidelines for the execution of the tests) are under continuous review, taking into account similar activities carried out by national and international bodies and progress in the understanding of the mechanisms of carcinogenesis. This project represents one of the contributions of the Agency to the International Programme on Chemical Safety (IPCS).

At present, eight national laboratories are involved in the network. The majority of studies involve the long-term testing of chemicals for carcinogenicity in rodents, although some deal with the development and validation of new tests in in-vivo systems.

A limited number of tests is also carried out at the Agency's laboratories, in particular on chemicals of considerable socio-economic importance, or when WHO is interested in the execution and coordination of tests on chemicals of primary importance for public health. For this latter purpose, the Agency has, in the past, tested DDT and, more recently, the antischistosomal drug Praziquantel, and is presently testing the molluscicide bis(tri-*n*-butyltin)oxide in several short-term tests.

*Mechanisms of Carcinogenesis*

In studies carried out at the Agency's laboratories in collaboration with national laboratories, it was shown that Burkitt's lymphoma cells always carry one of the following translocations: t(8);14, t(2);8, t(2);22, independently of the geographic origin of the patient. The finding that the transposition of a segment of chromosome 8 to an active region of the IG-locus carrying chromosomes 14, 2 and 22 suggests that Burkitt's lymphoma cells can be used to study the role of genetic transposition in carcinogenesis. Molecular studies have in fact indicated that the segment of chromosome 8 that is transposed in proximity to the immunoglobulin gene carries the 'myc' oncogene and that its mechanism of activation can therefore be investigated in these cells of human origin. The possible role of genetic transposition is presently also being studied in Ewing's sarcoma cells.

Another collaborative project has been started to evaluate possible genetic predisposing conditions. As a first step in this study, a collection of lymphoblastoid cell lines to provide a source of contitutional DNA will be established from members of families in which multiple cancer cases have arisen.

In other projects, the metabolism of carcinogens, and DNA damage and repair processes as critical determinants in the initiation of carcinogenesis are investigated. The *N*-nitrosamines, a group of environmental carcinogens with a high degree of organ- and species-specificity in their carcinogenic effect, have been used to determine the biological relevance of the kind of DNA damage produced by them, and to assess how the efficiency of repair of the DNA lesions they produce is related to the probability that *N*-nitrosamine-treated tissue and/or cells might develop into a tumour. Comparative in-vivo studies of the capacity of human and rodent tissue extracts to recover from DNA miscoding lesions like $O^6$-alkylguanine could contribute to the development of better criteria on which to base extrapolation of experimental animal data to human beings. Dose-responses in carcinogenesis and mutagenesis could also be better understood by examining at the cellular and molecular levels the modulation of DNA repair processes during continuous exposure to carcinogens.

Additional studies are being carried out on the mechanisms of tumour promotion. Previous and current studies show that the primary action of tumour promoter(s) like 12-*O*-tetradecanoylphorbol-13-acetate appears to be at the cell membrane surface, and to result in an inhibition of gap-junctional cell-cell communication and finally in alteration of gene expression. However, it has become evident that the mechanisms of action of the various classes of promoting agents are different and/or that their effect is dependent upon specific tissues or cell types. In these studies, attempts are being made to develop an in-vitro screening assay to detect compounds with tumour-promoting activity.

*Indicators of Individual Susceptibility*

The availability of individual (as opposed to group) measurements of human exposure to a potential carcinogen may prove critical in establishing a causal relationship between the agent and a cancer. Measurements of specific biological parameters, including immunological determinations of carcinogens and/or their cellular macromolecular adducts, may thus strengthen inferences from epidemiological studies by individualizing the characterization of exposure, in two ways: (1) by allowing measurements to be made at the individual (tissue and body fluids) rather than group level; and (2) by making measurements specific to a single chemical. In the Agency's laboratories, conventional antibodies have been prepared against aflatoxin $B_1$, and sensitive immunoassays for the detection of aflatoxin $B_1$ in body fluids and/or tissues are being developed.

Other studies are in progress to detect DNA modifications that are related to *N*-nitrosamine exposure, using a panel of high affinity antibodies in oesophageal tissues originating from people at high risk of developing tumours. Further studies are aimed at identifying the relevant DNA adducts induced by the human carcinogen vinyl chloride.

Additional studies are aimed at investigating which, if any, metabolic parameters and early markers of genetic damage determine individual susceptibility to chemically induced cancer. Genetic polymorphism, as expressed by individual drug handling capacity, is being studied, using strains of rats that are slow or fast metabolizers.

*Education and Training*

The Agency has an active programme in research training, emphasizing epidemiology and biostatistics and environmental carcinogenesis. Three to four courses a year are held in different WHO regions and in collaboration with the Regional Offices. In 1983, a workshop was held in Nairobi, on mutagenicity and carcinogenicity testing, in collaboration with UNEP and with the support of the University of Nairobi; a course on the epidemiology of cancer was held in Karachi; a course on statistical methods was given in Lyon; and a course on the epidemiology of cancer will be held on 14–27 November in Yaoundé, United Republic of Cameroon.

The fellowships programme is carried out in strict collaboration with the UICC and with WHO/HQ. Last year, of the 77 applications received, 57 were reviewed and 16 fellowships were awarded.

The Agency's publications programme has expanded successfully and now includes 56 volumes in its *Scientific Publications* series, and 33 volumes in the *Monographs* series.

*Funding*

The regular budget for 1983 was US$9 478 000.

*Personnel*

In June 1983, the Agency's staff of 150 consisted of 42 scientists, 44 technicians and 64 administrative and secretarial staff.

L. TOMATIS

# STUDIES ON ETIOLOGY AND PREVENTION

## 1. STUDIES ON GEOGRAPHICAL DISTRIBUTION AND TIME TRENDS

(*a*) *Cancer Incidence in Five Continents, Vol. V* (Dr C. S. Muir and Miss S. Whelan; in collaboration with Dr J. A. H. Waterhouse and Miss J. Powell, Birmingham and West Midlands Regional Cancer Registry, UK)

Following the publication of Volume IV of *Cancer Incidence in Five Continents* in October 1982, a first meeting to plan Volume V was held in Lyon in February 1983.

The majority of cancer registries contributed data for 1973-1977 for inclusion in Volume IV of the series; it was noted, however, that the 9th Revision of the ICD did not come into operation until 1979 and therefore data for 1978 were coded to the 8th Revision. Potential contributors to Volume V will be asked whether they would wish to omit 1978 or convert data for that year to the 9th Revision. Volume V will thus cover 1978 or 1979 to 1982; data will be requested by 1 January 1985, with a publication date of October 1986 in view.

(*b*) *Global burden of cancer* (Dr D. M. Parkin and Dr C. S. Muir)

With the increasing success in the prevention of a variety of infectious diseases and the concomitant improvement in life expectation, it is clear that by the year 2000 cancer will represent a major public health problem in both developed and developing countries. Estimates of the current

Table 1. Estimates of number of cases of common cancers expressed in thousands in the world around 1975 with rank order

| ICD-9 No. | Site | Males | | Females | | Total | |
|---|---|---|---|---|---|---|---|
| | | No. | Rank | No. | Rank | No. | Rank |
| 140-149 | Mouth & pharynx | 232.9 | 4 | 106.6 | 6 | 339.5 | 6 |
| 150 | Oesophagus | 194.0 | 6 | 102.3 | 7 | 296.3 | 7 |
| 151 | Stomach | 421.7 | 2 | 260.6 | 3 | 682.4 | 1 |
| 153-4 | Colon/Rectum | 251.2 | 3 | 255.6 | 4 | 506.9 | 4 |
| 155 | Liver | 182.5 | 7 | 76.9 | 9 | 259.2 | 8 |
| 162 | Bronchus/Lung | 464.3 | 1 | 126.7 | 5 | 591.0 | 2 |
| 174 | Breast (female) | – | – | 541.2 | 1 | 541.2 | 3 |
| 180 | Cervix uteri | – | – | 459.4 | 2 | 459.4 | 5 |
| 185 | Prostate | 197.7 | 5 | – | – | 197.7 | 10 |
| 188 | Bladder | 130.7 | 8 | 39.4 | 11 | 170.1 | 12 |
| 200-202 | Lymphatic tissue | 129.5 | 9 | 91.2 | 8 | 220.9 | 9 |
| 204-207 | Leukaemias | 100.3 | 10 | 75.4 | 10 | 175.7 | 11 |

global burden of cancer in terms of numbers of persons affected have been developed before embarking on projections for the future.

The recently published data in *Cancer Incidence in Five Continents* and material collected for the monograph on *Cancer Occurrence in Developing Countries* (see below) have been used, together with other published sources, to produce global estimates of the numbers of cancer cases that occurred around 1975. Twelve common tumour sites have been examined, and estimates were made of the cancer burden for each of the 24 geographic areas of the world for which the UN publishes population figures (Table 1). These estimates are based on the best data available. Although, in many instances, the figures at our disposal probably represent underestimates of the number of incident cases, these were used nonetheless as a basis for calculation rather than attempting to guess what the real incidence might have been.

In conjunction with the apparently universal fall in gastric cancer incidence and the rapid rise in lung cancer, the public health implications of these estimates are clear.

### (c) *Cancer in developing countries*

#### (i) *International collaborative study on relative frequency of cancer* (Dr D. M. Parkin, Miss S. Whelan and Mrs A. Arslan)

This project began in 1982 to bring together data on cancer occurrence from as many as possible of those centres in Africa, Asia and South America which do not have population-based registries that provide data for *Cancer Incidence in Five Continents.* Collaborating centres thus include newly created registries and those without information on the denominator populations from which their registered cases come. Numerous hospitals, cancer centres and pathology laboratories have also provided case series. The material will be presented in standardized format to permit comparison between the different centres, either as age-standardized relative frequency or, whenever possible, as estimated or minimum rates of incidence. Information about the nature of each centre and the source of cases has been collected by questionnaire and will be presented as a commentary to assist in the interpretation of the cancer patterns.

Almost all collaborating centres (approximately 55; see Fig. 1) had provided data by May 1983. Coding, checking, data entry and analysis will continue throughout 1983; it is anticipated that a monograph will be published in 1984.

#### (ii) *Support to cancer registries* (Dr D. M. Parkin and Dr C. S. Muir)

It is the policy of the Unit of Descriptive Epidemiology to support and encourage cancer registration activities, especially in centres in Africa, Asia, Oceania and Central America. During the past year visits were made to

*India,* to advise the Indian Council for Medical Research (Drs U. Luthra and L. D. Sanghvi, Indian Council of Medical Research, New Delhi) on organization and data collection procedures at the population-based cancer registries at Bangalore, Bombay and Madras and at hospital-based registries at Dibrugarh, Chandigarh and Trivandrum.

*Kuwait* (Dr Y. Omar, Director, Kuwait Cancer Control Centre, Kuwait) to advise the Gulf States on their collaborative registration scheme.

*Egypt* (Dr Ismael Khadry) to assess the feasibility of cancer registration in Tanta, Garbiah Governate, in the Nile delta.

Financial support has been continued to the Fiji Cancer Registry (Dr K. Singh, Pathology Department, CWM Hospital, Suva, DEB/81/023). The possibility of extending collaborative research agreements to other centres in Africa and Oceania is under discussion.

(iii) *Cancer registration in the Sudan* (Dr D. M. Parkin)

In 1983 the government of Sudan accepted proposals for a cancer control programme in that country, which will be supported by WHO (Cancer Unit/HQ and EMRO). An important element

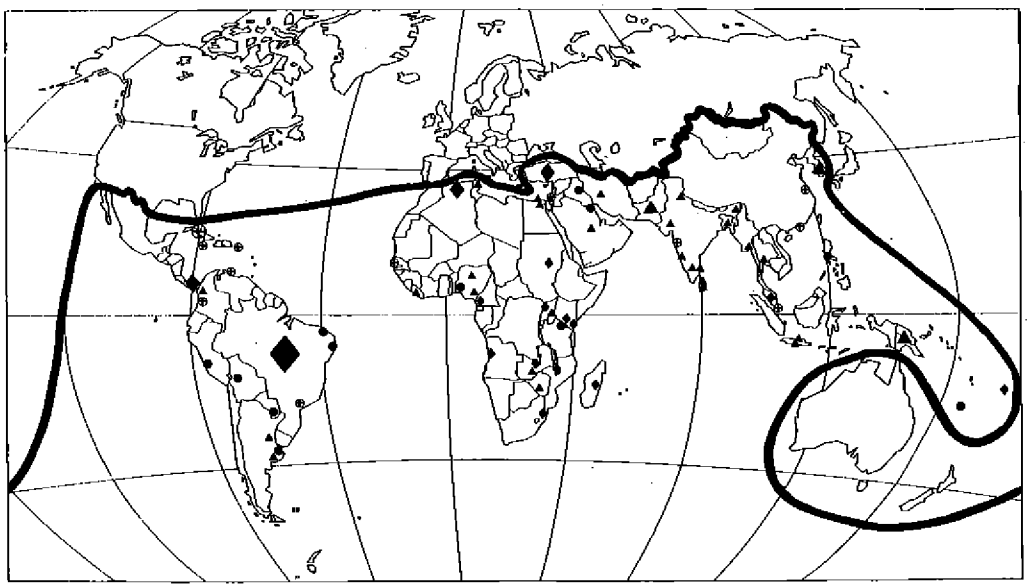

Fig. 1. Provisional participants in an international study of relative frequency of cancer. ⊕, population-based registry represented in *Cancer Incidence in Five Continents Vol. IV*; ●, population-based registry not represented in that publication; ▲, hospital registry; ▲, multi-centre hospital-based study; ◆, pathology data from a single laboratory or registry; ◇, pathology data from multi-centre or national study

of the proposed programme is establishment of the pattern of occurrence of certain common tumours, and monitoring the effects of programmes of early detection and treatment. This will involve improvement of cancer registration procedures; it is anticipated that the Unit of Descriptive Epidemiology will advise and support this part of the programme.

(*d*) *Time trends* (Mr M. Smans; in collaboration with Dr J. A. H. Waterhouse, Birmingham and West Midlands Regional Cancer Registry, UK)

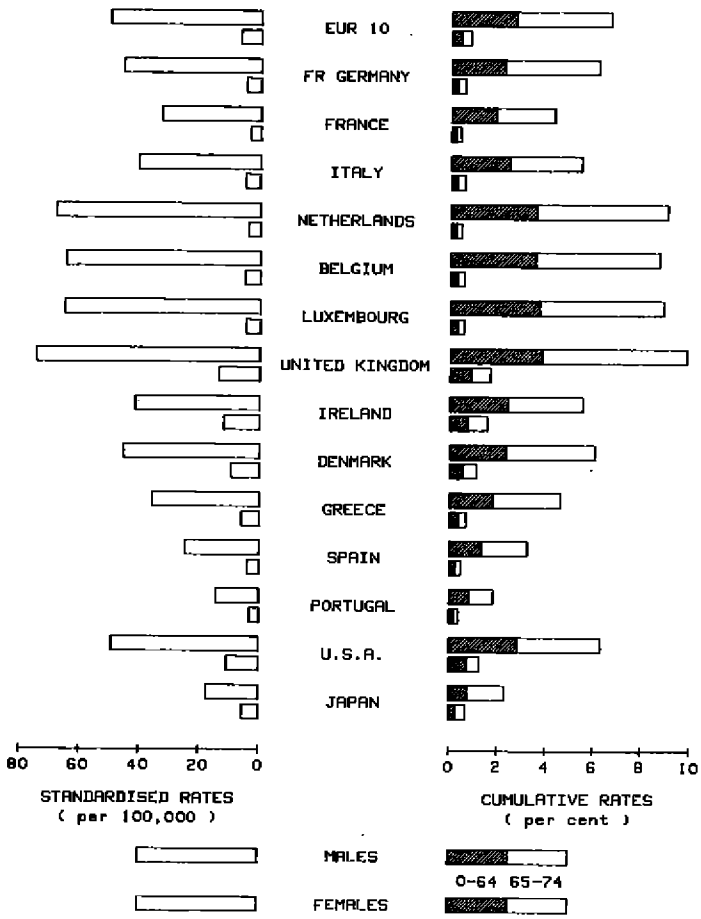


Fig. 2 Age-standardized and cumulative mortality rates for lung cancer in the countries of the European Economic Community and reference countries

Dr Waterhouse continues his work, as an Agency consultant, on a monograph describing observed trends, assessing the reality of changes recorded, and attempting to take into account the effect of changes of population structure and of patterns for other competing causes of death.

(*e*) *Social indicators of cancer in the European Economic Community* (Mr M. Smans)

The statistical division of the European Economic Community (EEC) (Mr D. Harris, Mr R. Walker) publishes a series of social indicators for member countries[1]. The Agency was asked to provide information on cancer mortality for the 10 EEC member states and for Spain and Portugal, two nations entry of which is under consideration. For comparison, information on Japan and the USA was also included. The mortality data were kindly made available to IARC by Dr H. Hansluwka, GES/WHO Headquarters. The colour graphs and histograms provided depicted the age-standardized death rates for the quinquennium 1970-1974 for the common sites of cancer and showed that, for example, the rates for lung cancer in Benelux and the United Kingdom were double those for France and Greece and four times greater than those for Portugal and Japan. The cumulative rates for the age-spans 0-64 and 0-74 years were also provided (Fig. 2). Time-trends in mortality from around 1950 to around 1977 were also given. A universal rise in lung cancer in people of both sexes is quite evident (with an encouraging flattening of male mortality in the United Kingdom), as is the widespread fall in gastric cancer mortality.

## 2. DETERMINATION OF ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

(*a*) *Carcinogenic risk of inhalable particles* (Dr R. Saracci and Dr L. Simonato)

(i) *Man-made mineral fibre production* (Dr R. Saracci, Dr L. Simonato, Dr J. Estève and Miss B. Charnay; in collaboration with Professor E. D. Acheson and Dr M. Gardner, MRC Environmental Epidemiology Unit, School of Medicine, Southampton, UK; Dr O. M. Jensen and Dr J. Olsen, Danish Cancer Registry, Copenhagen; Dr P. Westerholm, Swedish National Board of Occupational Safety and Health, Stockholm; Mr R. Maasing, Kabi AB Drug Co-operation, Stockholm; Dr A. Andersen, Norwegian Cancer Registry, Oslo; Dr P. A. Bertazzi and Dr C. Zocchetti, Clinic of Occupational Health Luigi Devoto, Milan, Italy; Dr R. R. Frentzel-Beyme and Dr J. Claude, German Cancer Research Centre, Heidelberg, FRG; and Dr L. Teppo, Finnish Cancer Registry, Helsinki; financed under contract with the Joint European Medical Research Board)

The results of the historical cohort study of the 13 European factories producing man-made mineral fibres were presented in a paper to be included in the proceedings of a Conference on Biological Effects of Man-made Mineral Fibres held in Copenhagen (WHO/EURO) in April 1982. Five main points emerge from the results of this epidemiological study, the first carried out on a broad international scale in occupational epidemiology:

[1] EUROSTAT (Statistical Office of the European Communities) (1980) *Social Indicators for EEC 1960-1978*, Luxembourg.

(1) The 13 factories in seven countries which it proved possible to include in the historical study cover sufficiently well the spectrum, particularly by production type, of the factories in the initial European roster of 72. However, the distribution by country tends to be more concentrated than in the initial roster (seven countries *versus* 15).

(2) The total cohort of workers ever employed and the total number of person-years of observation are quite large (more than 25 000 and more than 300 000, respectively); however, less than 10 000 person-years occurred 30 or more years after first employment. The average duration of employment is, for the cohort, about five years.

(3) Cumulative levels of exposure, as derived from airborne fibre concentration measurements under *present* production conditions, are low—generally in the range of 0.1–1-2 fibres x yrs/ml. However, environmental fibre concentrations *may* have been higher in the past, perhaps by one order of magnitude, as would be suggested by environmental data of a production line operating without binders[2]. As a term of comparison it can be recalled that in those studies of health effects of asbestos fibres in which fibre concentrations have been measured, cumulative exposures in the range of ten to several hundred fibres x yrs/ml have usually been reported. Low exposure to an agent, while advantageous and desirable for workers' health, may render a biological response induced by the agent (i.e., a carcinogenic effect) so inconspicuous as to be difficult or impossible to detect, even in a large study.

(4) No consistent departure of the observed numbers across factories from those expected on the basis of the experience of the general population is present for individual causes of death nor for individual cancer sites, with the exception of lung cancer (see next point). Only one death from mesothelioma was reported out of a total of 303 353 person-years computed for males and females.

(5) When data from all factories are pooled (data for individual factories are displayed in Table 2), lung cancer risk is increased 30 years after first employment, with a SMR of 192 (95% confidence interval; 117-307).

It is at present difficult to interpret this finding. Some elements point towards a possible causal role of exposure to man-made mineral fibres: the excess occurs at a site (lung cancer) and at a time (several decades after first employment) in which an effect could be expected to appear. Some other elements, however, fail to support a causal role of this exposure. There is no relation to cumulative exposure. Some excess appears irrespective of the type of exposure (rockwool, glasswool, continuous filament), in spite of the different average respirable airborne levels in the three processes. When data on lung cancer incidence are looked at in a similar way at the individual factory level, no consistent excess across factories is found, although this may be due to the very sparse data on incidence (in contrast to mortality). Finally, as in most historical cohort studies, the interpretation of the results is limited by the absence of information on occupational and non-occupational confounding factors such as previous occupational history and smoking habits.

Further epidemiological and environmental investigations, with particular attention to data on past exposure and confounding factors, are required before a definitive interpretation of these findings can be formulated.

A preliminary protocol for a five-year (1978–1982) extension of the follow-up of workers and for an assessment of past environmental conditions at these plants has been drawn up and circulated among the national collaborators for discussion and finalization. This extension of the study will be begun late in 1983.

[2] Ottery J. (1981) *Report on the Environmental Investigation at Rockwool A/B, Skovde (IOM Internal Document No. BP. 31075/2/B(4)13.1)*, Edinburgh, Institute of Occupational Medicine.

Table 2. Mortality from cancers of the trachea, bronchus and lung by factory and by time since first employment (males)

| Factory | 0-19 years OBS/EXP | SMR | 20-29 years OBS/EXP | SMR | 30 + years OBS/EXP | SMR | Total OBS/EXP | SMR |
|---|---|---|---|---|---|---|---|---|
| B (Glasswool) | 27/24.19 | 112 | 8/9.18 | 87 | 2/0.97 | 206 | 37/34.34 | 108 |
| D (Glasswool) | 1/3.30 | 30 | 2/2.37 | 84 | 2/1.35 | 148 | 5/7.02 | 71 |
| F (Glasswool) | 2/2.73 | 73 | 0/1.29 | 0 | 0/0.16 | 0 | 2/4.18 | 48 |
| L (Glasswool) | 0/1.02 | 0 | 0/0.31 | 0 | 0/0.09 | 0 | 0/1.42 | 0 |
| C (Rockwool) | 11/16.76 | 66 | 5/2.74 | 182 | 2/0.89 | 225 | 18/20.39 | 88 |
| G (Rockwool) | 3/2.63 | 114 | 0/0.58 | 0 | 0/0.02 | 0 | 3/3.23 | 93 |
| H (Rockwool) | 3/0.62 | 484 | 2/0.33 | 606 | 0/0.20 | 0 | 5/1.15 | 435 |
| I (Rockwool) | 0/0.58 | 0 | 0/0.10 | 0 | 0/0.04 | 0 | 0/0.72 | 0 |
| K (Rockwool) | 2/1.03 | 194 | 0/0.49 | 0 | 0/1.19 | 0 | 2/2.71 | 74 |
| M (Rockwool) | 2/1.82 | 110 | 1/1.18 | 85 | 3/0.76 | 395 | 6/3.76 | 160 |
| O (Rockwool) | 6/6.38 | 94 | 4/4.26 | 94 | 6/2.58 | 233 | 16/13.22 | 121 |
| J (Continuous filament) | 5/3.98 | 126 | 0/0.42 | 0 | 0/0.11 | 0 | 5/4.51 | 111 |
| N (Continous filament)[a] | 6/3.97 | 151 | 2/1.52 | 132 | 2/0.51 | 392 | 10/5.99 | 167 |
| TOTAL | 68/69.01 | 98 | 24/24.76 | 97 | 17/8.87 | 192 | 109/102.57 | 106 |

[a] Glasswool predominant until 1962, when discontinued.

(ii) *Man-made mineral fibre users* (Dr G. Engholm, Dr R. Saracci and Dr N. E. Day; in collaboration with Dr G. von Schmalensee and Dr A. Englund, Bygghälsan, The Swedish Foundation for Occupational Safety and Health in the Construction Industry, Stockholm)

This investigation has been carried out as a case-control study based on the follow-up of a cohort of some 135 000 Swedish construction workers. Some results were presented at the conference at WHO/EURO in Copenhagen in April 1982. The average length of follow-up was only 5.5 years, however, and the stability of relative risk estimates for heavily exposed subjects was poor. An extension of the follow-up is now being carried out which will increase the number of cases of respiratory cancer by more than 50%.

(iii) *Mesothelioma in central Turkey* (Dr R. Saracci and Dr L. Simonato; in collaboration with Dr Y. I. Baris and Dr M. Artvinli, Department of Chest Diseases, Hacettepe University, Ankara, DEB/82/014; and Dr J. Skidmore, MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, Wales, UK)

The epidemiological and environmental data from a four-year survey in four villages (Karlain, Karlik, Sarahidir, Tuzkoy) in central Turkey are being analysed with a view to preparing a comprehensive paper, including environmental and epidemiological data, on the endemic of mesothelioma. The evidence so far collected confirms the high occurrence of pleural and pulmonary malignant neoplasms in three of the four villages and indicates a common exposure to zeolite fibres as the most probable cause of the disease. Fibre characteristics, however, need further analysis, and the assessment of exposure must be improved in order to ascertain beyond doubt the causative role of life-time exposure to zeolite fibres. To this end, lung specimens from sheep living in the villages under study are being collected and analysed for total amount of fibres accumulated in the lung tissues and for fibre characteristics.

(iv) *Silicosis and lung cancer* (Dr L. Simonato and Dr R. Saracci)

Silica dust is one of the major contaminants in the occupational environment, and its health effects, particularly on the respiratory system, have been known for a long time. The hypothesis that silica dust could also increase the risk of lung cancer has been investigated, with conflicting results. Cigarette smoking as a confounding factor, and non-neoplastic respiratory diseases as competing causes of death, seem to be the main obstacles to making a definitive evaluation of the problem.

An ad-hoc Working Group, composed of European researchers interested in health effects of silica dust, convened in Lyon on 30 June 1983 to examine the feasibility of carrying out collaborative studies on the subject. The discussion focused on the possibility of using three main sources of information: (1) records of workers compensated for silicosis; (2) routinely collected mortality data on occupational exposure; and (3) cross-sectional studies of workers exposed to silica dust to exploit the possibility of following up historical cohorts.

The availability of information and the feasibility of carrying out epidemiological studies are now being evaluated both at the national level and at the Agency, and a decision will be reached later in 1983.

(*b*) *International study of people exposed to dioxin-contaminated substances* (Dr R. Saracci, Dr J. Wahrendorf, Mr J. Wilbourn and Dr P. Honchar; financed by the National Institute of Environmental Health Sciences of the USA, through Contract No. NO1-ES-1-5009)

The initial decision to establish a registry of people outside the US exposed to phenoxy herbicides was motivated by several factors. The mounting evidence for adverse health effects of phenoxy herbicides and their contaminants was summarized in 1978 by an international group of scientists who met at the Agency and recommended long-term follow-up, and particularly the establishment of registries, of exposed persons[3]. In 1979, the US National Institute for Occupational Safety and Health began actively collecting work history records and exposure information on US industrial workers involved in the synthesis of phenoxy herbicides and chlorophenols for a registry to be used eventually for epidemiological study. Of central interest to the Agency has been the recent epidemiological evidence, largely stemming from three case-control studies from Sweden, of possible human carcinogenicity of these materials. As this issue is unresolved and open to debate, the need was perceived for further, timely and adequate epidemiological investigation to clarify it, if possible definitively.

A feasibility assessment was carried out in 1982 with the following aims:

(1) to identify, learn about, and assess the suitability of cohorts (outside the US) with defined exposure to phenoxy herbicides and/or chlorophenols for inclusion in a registry and for subsequent epidemiological study; and
(2) to identify simultaneously in each country in which there is at least one potential cohort a scientist who is interested in participating in this project as an Agency collaborator and also to learn from these contacts about other potential cohorts.

[3] International Agency for Research on Cancer (1978) *Long-term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans (IARC Internal Technical Report No. 78/001)*, Lyon.

Two basic foci were defined for the proposed Agency registry and, hence, for the feasibility assessment: first, the chemical substances of interest and, second, the type and source of exposure for persons to be entered in the registry. It was decided to identify people exposed to the following substances: 2,4,5-trichlorophenoxyacetic acids and esters, trichlorophenol, pentachlorophenol, 2,4-dichlorophenoxyacetic acids and esters and (4-chloro-2,2-methylphenoxy)acetic acids and esters. The rationale for considering these substances is as follows: the first three are known to be contaminated during their synthesis by isomers of dioxin; 2,4,5-trichlorophenoxyacetic acids and trichlorophenol, in particular, contain the highly toxic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). 2,4-Dichlorophenoxyacetic acids also carry some contaminants, but these are less well known at this time. (4-Chloro-2,2-methylphenoxy)acetic acids are not known to be contaminated with dioxin isomers, but they are closely related phenoxy herbicides. Also important is the fact that exposure to all of these substances has been associated with an excess risk of soft-tissue sarcoma and lymphoma in the case-control studies conducted in Sweden.

It was decided that the primary focus would be on people with occupational exposure through work at the synthesis of these substances. Cohorts with occupational exposure through the use of these materials (e.g., sprayers) would be considered secondarily. The focus on occupational exposure is expected to maximize the amount and quality of the data to be considered for inclusion in the registry. Occupational cohorts are more likely to be recorded in some kind of work history record, which can be used as a historical source of information for each person, for the substances worked with, for duration, type of job and exposure and, if present, confounding exposure(s). In contrast, the exposure information on people with non-occupational or environmental contact with the substances of interest is less easily defined, even when the subjects live near, or are at present in the vicinity of, a chemical plant producing these substances or an area where the chemicals have been intentionally or unintentionally applied.

The feasibility assessment was carried out through multiple contacts with potentially interested investigators, and it involved, as a rule, a site visit to workplaces and to research institutions. Results indicate that for 14 factory cohorts in 10 countries no obstacle to inclusion in an Agency registry can be foreseen, while for an additional 10 factories open problems remain. Also, in view of the relatively small size of the cohorts involved, inclusion of users (e.g., sprayers) has been considered. The results of the feasibility study and the plan of work will be examined at a meeting in October 1983, which will include scientists from the Agency, the US National Institute of Environmental Health Sciences as well as potential national collaborators. At the meeting, decisions will be taken on how to proceed with this project in the light of the results of the feasibility study.

(*c*) *Case-control study of long-term effects of pesticides on human health in Colombia* (Dr N. Muñoz and Dr N. Day; in collaboration with Dr M. Restrepo and Dr A. Giraldo, National Institute of Health, Bogota; Dr J. Davies and Dr C. Pfaffenberger, Department of Epidemiology and Public Health, University of Miami, FL, USA; and Dr J. Litvak, WHO Regional Office for the Americas, Washington DC; financed by the US Environmental Protection Agency through the WHO Regional Office in Washington DC)

During the prevalence survey carried out in 1981–1982, a total of 561 children were reported by their parents as being malformed. Of these children, 52 are dead, and 400 had been examined by a geneticist up to May 1983. Two controls matched by the age of the mother at pregnancy and birth order have been selected for each malformed child. Of 1105 controls selected, 800 children have

been examined by a paediatrician; in 78%, there was agreement between the report of the parents and the results of the physical examinations. A review of all clinical records of cases and selected controls will be carried out in July 1983 by Dr L. Holmes of the Massachussetts General Hospital.

Up to May 1983, information on the type of pesticide and amount and pattern of use had been collected for 40 of 58 floriculture companies which participated in the prevalence survey. The ten pesticides used most widely were Captan, Benomyl, Mancozeb, Chlorothalonil, Methomyl, Tetradifon, Propineb, Pirimicarb, Dicofol and Dienochlor. The results of the pilot study on Captan are not yet available.

(*d*) *Feasibility approach to a multi-centre cohort study on smoking, serum cholesterol and diet* (Dr J. Wahrendorf)

A project entitled 'Multinational Monitoring of Trends and Determinants in Cardiovascular Disease' (MONICA) is being developed at WHO Headquarters, Geneva. Part of the project, in which some 30 centres all over the world are participating, is the conduct of standardized population-based surveys on the prevalence of certain risk factors such as smoking, serum cholesterol and, more generally, dietary habits. It is being investigated whether it would, in some areas, be feasible to follow up individuals enrolled in these surveys through cancer registries for their subsequent cancer experience. Such a multinational, population-based and prospective cohort study could investigate life-style-related etiological hypotheses of cancer.

(*e*) *International collaboration in observational studies (the SEARCH programme)* (Dr A. Walker, Dr R. Saracci and Dr N. Day)

A network of locally funded centres collaborating within an organizational framework centred at the Agency has been established as the first component of the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH). Centres in Adelaide, Australia, Toronto, Canada, Utrecht, The Netherlands, and Warsaw have joined in a collaborative study of cancers of the pancreas, bile duct and gall-bladder (see p. 58). The advantages of the collaboration are that it permits concurrent replication of important findings; it allows the investigation of cancers that cannot ordinarily be studied in any one centre; it gives investigators the opportunity to share experience in the execution of closely coordinated research protocols; and it allows the Agency to participate intimately in the research programmes of a number of major centres of epidemiological expertise. The network is expected to grow and to diversify in terms of the kinds of populations among whom research is being carried out and of the number of cancer sites to be studied.

The SEARCH programme represents the coordinating unit for the Agency's planned collaborative case-control studies in Singapore of cancers of the breast and colon, and the planned follow-up of opium addicts in Singapore.

Questions relating to the methodology of case-control studies are being actively studied under the SEARCH programme. The collaborating group involved in cancers of the pancreas, bile duct, and gall-bladder is assessing the determinants of reliability in proxy interviews for diet and personal habits (see p. 64), and a conference to evaluate the optimum methods of eliciting occupational exposure histories is planned for early 1984 (see p. 47).

*(f) Analysis of environmental carcinogens and analytical quality assurance*

(i) *International mycotoxin check sample programme* (Dr M. Friesen, Mrs L. Garren and Miss Y. Granjard; supported in part by the Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme and the Mycotoxins Working Group of the IUPAC Commission on Food Chemistry)

This programme provides an opportunity for laboratories engaged in the analysis of mycotoxins in foodstuffs to compare their own analytical results with those of other laboratories around the world[4, 5, 6]. Participants analyse identical portions of a homogeneous food sample for a given mycotoxin using the analytical method of their choice. Results are collected and evaluated statistically at the Agency before redistribution to the individual laboratories. At present, the programme, which is free of charge to participants, is carried out once each year. A summary of results obtained over the past several years was published recently[7].

This year, 163 laboratories in 44 countries participated in the analysis of aflatoxins $B_1$, $B_2$, $G_1$, and $G_2$ in maize (corn) and peanut products and/or aflatoxin $M_1$ in lyophilized milk. A subgroup of laboratories also participated as part of the FAO/WHO Food and Animal Feed Monitoring Programme to help assure the quality of results generated by collaborating centres in this programme around the world.

(ii) *Methods of analysis for carcinogens in environmental samples* (Dr M. Castegnaro and Miss M. C. Bourgade; in collaboration with Dr C. L. Walters, British Food Manufacturing Industries Research Association, Leatherhead, UK; The Association of Official Analytical Chemists (AOAC); and Dr R. Massey, Ministry of Agriculture, Fisheries & Food, Norwich, UK; partly supported by IUPAC)

The results of the collaborative study on the method of analysis for total *N*-nitroso compounds developed by Dr Walters' group have been evaluated. Although there was wide variability among the results, two conclusions could be drawn: firstly, examination of the calibration curve shows that a linear response was obtained over the range applicable to the Thermal Energy Analyzer in all laboratories; secondly, those laboratories with experience of the method using the Thermal Energy Analyzer obtained results comparable with the spiking level. The description of the method has therefore been revised (in collaboration with Dr Walters' group and with Dr Massey), and this method will now be tested in a study involving the Agency and those two laboratories.

(iii) *Ochratoxin A in foodstuffs in relation to nephropathy and bladder cancer* (Dr M. Castegnaro; in collaboration with Dr I. N. Chernozemsky and Dr T. Petkova, National Centre of Oncology, Sofia; DEC/81/024)

Balkan endemic nephropathy is a fatal renal disease affecting inhabitants of rural areas of Bulgaria, Romania and Yugoslavia. Its etiology remains so far unknown. A large number of patients with this condition develop tumours of the urinary system; and because of some alleged

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[4] Friesen, M. D. & Garren, L. (1982) *J. Assoc. off. anal. Chem.*, **65**, 855–863.
[5] Friesen, M. D. & Garren, L. (1982) *J. Assoc. off. anal. Chem.*, **65**, 864-868.
[6] Friesen, M. D. & Garren, L. (1983) *J. Assoc. off. anal. Chem.*, **66**, 256–259.
[7] Friesen, M. D. (1983) In: Stoloff, L., Castegnaro, M., Scott, P., O'Neill, I. K. & Bartsch, H., eds, *Environmental Carcinogens, Selected Methods of Analysis*, Vol. 5, *Some Mycotoxins (IARC Scientific Publications No. 44)*, Lyon, International Agency for Research on Cancer, pp. 85–106.

similarities of this disease to ochratoxin-induced porcine nephropathy[8], attempts have been made to elucidate a possible causal role of ochratoxin A in the human conditions.

Preliminary results have indicated that ochratoxin A is frequently present in foodstuffs from an area of Yugoslavia where nephropathy is endemic[9, 10]. Ninety-two samples (200–300 g) of beans, maize and wheat flour were collected during the period February-March 1982 from individual households. Sixty-five of them were from families of patients with Balkan endemic nephropathy and/or urinary system tumours, who inhabited villages of Vratza District, Bulgaria with high incidences of endemic nephropathy. The other 27 samples were taken from families that inhabited villages of a non-endemic district of Bulgaria.

The samples were analysed for ochratoxin A contamination according to a published procedure[11]. In total, 92 samples were analysed, and ochratoxin A was found in 10, all of which originated from 65 samples collected from endemic families of Vratza District (Table 3). The range of concentrations of ochratoxin A was 25–27.2 μg/kg in the bean samples and 25–35 μg/kg in the maize samples. The finding that no ochratoxin A was present in the wheat flour samples collected from the same region may be due to the fact that the samples of beans and maize collected from families of patients with Balkan endemic nephropathy and/or urinary system tumours in the endemic area of Vratza Districts were produced locally by each family in sufficient quantity for one year and were stored in the households, while the wheat flour was purchased.

Thus, ochratoxin A was detected in about 17.5% of the samples produced and used by the population in an area where Balkan endemic nephropathy and a high incidence of urinary system tumours are prevalent. This finding indicates the need for further investigations, including further analyses of samples from families of non-endemic areas of Bulgaria.

Table 3. Ochratoxin A contamination of some cereals collected in endemic and control areas of Bulgaria

| Cereal | No. of contaminated samples/ total analysed (% contaminated) Endemic area | Control area |
|---|---|---|
| Beans | 4/24 (16.7%) | 0/6 (0%) |
| Maize | 6/24 (25.0%) | 0/7 (0%) |
| Wheat flour | 0/9 (0%) | 0/14 (0%) |
| Total | 10/57 (17.5%) | 0/27 (0%) |

[8] Krogh, P. (1974) In: Puchlev, A., ed., *Endemic Nephropathy*, Sofia, Bulgarian Academy of Sciences, pp. 266–277.
[9] Krogh, P., Hald, B., Plestina, R. & Ceovic, S. (1977) *Acta pathol. microbiol. scand.*, **85**, 238–240.
[10] Pavlovic, M., Plestina, R. & Krogh, P. (1979) *Acta pathol. microbiol. scand.*, **87**, 243–246.
[11] Stoloff, L., Castegnaro, M., Scott, P., O'Neill, I. K. & Bartsch, H., eds (1982) *Environmental Carcinogens – Selected Methods of Analysis*, Vol. 5, *Some Mycotoxins (IARC Scientific Publications No. 44)*, Lyon, International Agency for Research on Cancer, pp. 255–270.

(g) *Characterization of biologically active substances in complex mixtures of environmental origin*

(i) *Pyrolysis products of opium and their possible role in oesophageal cancer in Iran* (Dr M. Friesen, Mr C. Malaveille, Dr I. K. O'Neill, Mrs L. Garren, Mrs A. Hautefeuille, Dr J. Cabral, Mrs D. Galendo, Mr A. Barbin, Mr J. C. Béréziat, Dr G. Mahon, Dr N. Day and Dr H. Bartsch; in collaboration with Dr I. Chouroulinkov, Institute of Scientific Research on Cancer, Villejuif, France; Dr H. J. Evans, Unit of Clinical and Population Cytogenetics, Medical Research Council, Edinburgh, UK; Dr G. Grimmer, Biochemical Institute for Environmental Carcinogens, Ahrensburg, FRG; Professor U. Mohr, School of Medicine, Hanover, FRG; Professor M. Roberfroid, Laboratory of Biotoxicology, Catholic University of Louvain, Brussels; Dr K. Szendrei, Department of Pharmacognosy, University Medical School, Szeged, Hungary; Dr V. Turusov, Oncological Research Centre, Moscow; Dr C. Gorodetzky, National Institute on Drug Abuse, Lexington, KY, USA; and Dr D. Fraisse and Dr Q. T. Pham, National Centre for Scientific Research, Vernaison, France; DEC/82/022)

Collaborative laboratory investigations are under way to identify and characterize the major mutagenic compounds present in smoke condensates of opium and its major alkaloid, morphine. This work derives from a series of epidemiological and chemical field studies[12, 13], undertaken in a region of north-east Iran where oesophageal cancer is exceedingly common in both men and women. The studies indicated that the incidence is associated (although causality has not been established) with the ingestion of opium pyrolysates, excessive consumption of hot tea and a restricted diet, in particular, riboflavin deficiency and a low intake of protein[14]. More recent results[15] on the distribution of morphine metabolite concentrations in the urine of subjects from the high- and low-risk areas in Iran show that appreciable levels ($> 10$ µg/ml) occur with high prevalence in the urine of both males and females from the high-risk area: relatively low prevalences were observed among males and females from the low-risk area.

Results of attempts to characterize the compounds responsible for the biological activity of opium and morphine pyrolysates are summarized below:

(1) *Mutagenicity* in Salmonella typhimurium[16]: Samples of opium pipe scrapings, called *sukhteh* in the region of Iran where collected, but not crude opium, were shown to contain pro-mutagens that produced mainly frameshift mutations in *Salmonella typhimurium* strains TA1538 and TA98 after metabolic activation. Pyrolysis of opium and morphine yielded smoke condensates with mutagenic activities 10 and 100 times higher, respectively, than that of the *sukhteh* samples tested. Aromatic amines or heterocyclic (nitrogen-containing) aromatic compounds appear to be the major mutagenic constituents.

(2) *DNA damage and repair in mice and hamsters* in vivo: The alkaline elution assay, as adapted in our laboratory[17], was used to evaluate the DNA damage induced by morphine pyro-

[12] Mahboubi, E., Kmet, J., Cook, P. J., Day, N. E., Ghadirian, P. & Salmasizadeh, S. (1973) *Br. J. Cancer*, **28**, 197–214.

[13] Joint Iran-IARC Study Group (1977) *J. natl Cancer Inst.*, **54**, 1127–1138.

[14] Day, N. E., Malaveille, C., Friesen, M. & Bartsch, H. (1983) In: Stich, H., ed., *Carcinogens and Mutagens in the Environment*, Vol. II, *Naturally Occurring Compounds*, Boca Raton, FL, CRC Press.

[15] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, p. 35.

[16] Malaveille, C., Friesen, M., Camus, A.-M., Garren, L., Hautefeuille, A., Béréziat, J.-C., Ghadirian, P., Day, N.E. & Bartsch, H. (1982) *Carcinogenesis*, 3, 577–585.

[17] Barbin, A., Béréziat, J.-C. & Bartsch, H. (1983) *Carcinogenesis*, 4, 541–545.

lysate. Syrian golden hamsters were treated by intraperitoneal injection with either a single dose (ranging from 100 to 500 mg/kg body weight) or four repeated doses of 125 mg/kg. C57B1 mice received a single dose of 20 mg/kg pyrolysate. DNA from the liver was analysed 4 h (mice and hamsters) or 18 h (hamsters) after treatment. In contrast to the results obtained with morphine pyrolysates in other test systems, no strand breakage was observed.

(3) *Chromosomal damage in CHO cells and human peripheral blood lymphocytes* in vitro[18]: The induction of sister chromatid exchange by *sukhteh*, opium pyrolysate and morphine pyrolysate was compared with that of cigarette smoke condensate. All pyrolysates increased the frequency of sister chromatid exchanges, and this was further increased by the inclusion of a 9000 × *g* supernatant from liver in the test protocol. In CHO cells, the rank order of potency on a weight basis was: morphine pyrolysate > opium pyrolysate > cigarette smoke condensate > *sukhteh*.

(4) *Tests for initiation and promotion*[19]: *Sukhteh*, opium pyrolysate and morphine pyrolysate were applied to the dorsal skin of female CDI mice three times weekly for 50 weeks. No tumour was found in mice given 2.88, 0.29 and 1.44 mg of each substance per animal; however, positive results were observed when 2.4 mg morphine pyrolysate were given to mice by two dorsal applications followed by repetitive applications sof 12-*O*-tetradecanoylphorbol-13-acetate. Transformed foci were induced *in vitro* in Syrian hamster embryo cells by morphine pyrolysate (1.3 μg/ml), opium pyrolysate (20–50 μg/ml) and *sukhteh* (50–70 μg/ml). No morphological transformation was observed with C3H10T½ cells.

(5) *Effect on drug-metabolizing enzymes*: Intraperitoneal administration of *sukhteh*, opium pyrolysate and morphine pyrolysate to male NMRI and C57B1/6 mice decreased the cytochrome P-450 content and benzo[*a*]pyrene-hydroxylase and aldrin monoxygenase activities in the liver. Antipyrine half-life (as an indicator of hepatic drug-metabolizing capacity) was therefore assayed in 200 individuals living in north-east Iran; large inter-individual variation was observed. Although minor differences were seen by age and sex, none could be related either to the use of opium, as indicated by the presence of morphine metabolites in the urine, or to place of residence, characterized as high- or low-risk areas for cancer of the oesophagus. These results are being prepared for publication.

(6) *Oral administration to mice and pregnant rats*: Experiments are in progress in which groups of 30 male and 30 female C57B1/6 mice, six weeks old, have received morphine pyrolysate in arachis oil orally once weekly for life at dose levels of 0, 2.5, 5 and 10 mg/kg. Morphine pyrolysate in arachis oil was also administered orally to female BDVI rats on the 15–19th day of gestation at a dose of 10 mg/kg bw. Progeny from treated and control groups are under observation.

(7) *Subcutaneous injection into mice:* Mice were injected subcutaneously with morphine pyrolysate, opium pyrolysate and *sukhteh* in olive oil. Preliminary results indicate two mammary carcinomas in the *sukhteh* group, one sarcoma in the morphine pyrolysate group, one unspecified tumour in the opium pyrolysate group and none in the control group. The results are under final evaluation.

(8) *Intratracheal instillation in hamsters*: Results from experiments involving intratracheal instillation of morphine pyrolysate, opium pyrolysate and *sukhteh* in hamsters are under final histological analysis.

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[18] Perry, P. E., Thomson, E. J., Vijayalaxmi, Evans, H. J., Day, N. E. & Bartsch, H. (1983) *Carcinogenesis*, 4, 227–230.

[19] Lasne, C., Sala, M. & Chouroulinkov, I. (1983) In: Börszönyi, M., Day, N., Lapis, K. & Yamasaki, H., eds, *Models, Mechanisms and Etiology of Tumour Promotion (IARC Scientific Publications No. 56)*, Lyon, IARC (in press).

(9) *Isolation and structural elucidation of pure, biologically active compounds in opium pyrolysates*: The major mutagenic substances in *sukhteh* and opium pyrolysates are probably nitrogen-containing aromatic compounds. Purification has been carried out by high-performance liquid chromatography of dichloromethane extracts of a basic aqueous solution of morphine pyrolysate. Nuclear magnetic resonance spectrometry ($^1$H-FTNMR) has shown that the three major compounds with mutagenic activity present in this fraction ($C_{16}H_{12}N_2O$: mol. wt, 248.0930; $C_{17}H_{15}NO$: mol. wt, 249.1159; and $C_{17}H_{14}N_2O$: mol. wt, 262.1115) contain a substituted hydroxyphenanthrene moiety as a common structural element. Final structural eludication and determination of the individual biological activities of these compounds are in progress.

(10) *Studies in humans*: Opportunities are being sought to study populations among whom opium use is or has been widespread, The follow-up of a cohort of 3000 individuals, registered as addicts in the 1950s in Singapore, is being undertaken. These data will link the cohort to the Singapore cancer registry and will be analysed principally as a proportional incidence study.

(ii) *Occurrence, formation and toxic effects of betel nut constituents* (Mr H. Ohshima, Mrs B. Pignatelli, Dr M. Friesen, Mr C. Malaveille, Mrs A. Hautefeuille, Miss M. C. Bourgade, Miss J. Michelon and Dr H. Bartsch; in collaboration with Professor U. Mohr, School of Medicine, Hanover, FRG; Dr A. Croisy, Faculty of Sciences, Curie Institute, Orsay, France; and Dr H. Stich, British Columbia Cancer Research Centre, Environmental Carcinogenesis Unit, Vancouver, BC, Canada)

Since the habit of chewing betel quids, particularly those containing tobacco, has long been associated with a high risk of cancer of the upper digestive tract in India and other countries of the Orient[20], and relatively high concentrations of nitrite/nitrate have been detected in saliva samples obtained from betel nut chewers[21], we initiated studies on the etiological role in oral cancer of in-vivo nitrosation of betel nut constituents. Two *N*-nitroso compounds, *N*-nitrosoguvacoline and *N*-nitrosoguvacine, have been identified as major products following nitrosation of betel nuts[22]. In a number of kinetic studies, it was found that formation *in vitro* of both nitrosamines was proportional to the concentration of betel nut and to the square of nitrite concentration; the optimal pH for formation of these compounds was 3.5–4. These results coincide with kinetic data reported for other secondary amines. On the basis of these findings, a long-term feeding study in hamsters involving simultaneous administration of nitrite and betel nut powder is being undertaken in collaboration with Professor Mohr.

A gas chromatographic method for determining betel nut-specific alkaloids (arecoline, arecaidine, guvacoline and guvacine) has been developed in this laboratory. The alkaloids, except for arecoline, were converted to their trimethylsilyl derivatives, which could be separated on an OV–17 column and detected by flame ionization. Arecoline was determined without derivatization. The method is being used to determine the level of alkaloids present in betel nuts and to study the release of these compounds from betel nut in the presence or absence of lime under in-vitro conditions that simulate betel-quid chewing.

The effects of different phenolic fractions (total aqueous extract, tannins, flavonoids, catechins) prepared from betel nuts on the rate of nitrosation of proline and diethylamine have also

[20] Khanoklar, V. R. (1950) *Acta unio int. cancrum*, **15**, 881–890.
[21] Shivapurkar, N. M., DeSouza, A. V. & Bhide, S. B. (1979) *Food Cosmet. Toxicol.*, **18**, 277–281.
[22] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, p. 30.

been investigated[23]. *In vitro*, all the extracts exerted both catalytic and inhibitory effects on the formation of *N*-nitrosodiethylamine and *N*-nitrosoproline depending on the pH and the ratio of the concentrations of betel nut extracts to nitrite: at pH 4, catalysis of *N*-nitrosoproline formation was observed with low concentrations of the extracts, while higher concentrations inhibited the nitrosation; at pH 1.9 only inhibitory effects were observed with all the extracts, which increased with increasing concentration of polyphenolics. By comparing the amount of *N*-nitrosoproline excreted in the urine of rats treated with precursors (proline, nitrite), with or without a polyphenolic fraction, their modifying effects *in vivo* were also assessed and found to be similar to those *in vitro*, although the effects *in vivo* were in general 42 to 85% less.

After ingestion of various betel nut extracts (total aqueous, tannin and catechin fractions) together with proline and nitrate[24] by two human volunteers, a relatively strong inhibition of *N*-nitrosoproline formation was observed with each of the extracts[25].

(iii) *Characterization of active principles in local plants in Pakistan* (Dr S. Riazuddin, Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan; DEC/80/001)

An aqueous extract of green '*naswar*' from Peshawar was shown to be mutagenic in a bacterial mutagenicity test system. Samples of this drug were extracted with petroleum ether and resolved by a combination of column chromatography and preparative thin-layer chromatography to isolate a chemical compound with a molecular composition of $C_{34}H_{44}O_9$. This compound was active in *Salmonella typhimurium* TA98 and TA1535 in the presence of liver microsomal fractions from Aroclor-induced rats. There was no activity in tester strains TA100, TA1537 or TA1538.

An insect repellent compound isolated from rhizomes of a local plant (*Sasurea lappa*) has been identified as a sesqueterpene. This compound was active against tester strains TA98 and TA1535 and required metabolic activation for its mutagenic activity. Labelled sesqueterpene will be used to study the interaction between the chemical and DNA at the molecular level.

(*h*) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (Dr H. Vainio, Mr J. Wilbourn, Ms L. Haroun, Mrs C. Partensky and Mrs I. Peterschmitt)

The objective of this project is to identify, on the basis of all published epidemiological and experimental data relevant to carcinogenicity and human exposure, chemicals, groups of chemicals and exposures to complex mixtures that may pose a carcinogenic risk to humans. Data on selected compounds and exposures are summarized and evaluated by international working groups of experts in chemical carcinogenesis and related disciplines, and their deliberations are published as a volume of the *IARC Monographs* series. The evaluations are intended to assist national and international authorities in formulating decisions concerning preventive measures. Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. Since 1972, the US National Cancer Institute has provided financial and scientific support to this programme.

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[23] Stich, H. F., Dunn, B. P., Pignatelli, B., Ohshima, H. & Bartsch, H. (1984) In: N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)* (in press).

[24] Ohshima, H., Pignatelli, B. & Bartsch, H. (1981) In: Magee, P. N., ed., *Nitrosamines and Human Cancer (Banbury Report No. 12)*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 297–317.

[25] Stich. H. F., Stich, W., Ohshima, H., Pignatelli, B., Michelon, J. & Bartsch, H. (1983) *J. natl Cancer Inst.* (in press).

Many units within the Agency contribute to the planning and implementation of the working groups. During the last year, expertise in epidemiology was provided by Drs R. Saracci, L. Simonato, M. Parkin and D. Zaridze; in experimental pathology, toxicology and mutagenesis by Drs R. Montesano, H. Bartsch, J. R. P. Cabral, A. Likhachev and H. Yamasaki; in analytical chemistry by Drs I. K. O'Neill and M. Friesen; and in statistical aspects of data analysis by Drs J. Wahrendorf and G. Mahon.

During the year under review, three working groups were convened in Lyon, whose deliberations and conclusions resulted in Volumes 31, 32 and 33 of the *Monographs*[26, 27, 28].

Volume 31 comprises 21 monographs on food additives, feed additives (veterinary drugs added to animal feeds) and naturally occurring substances. The data on carcinogenicity in experimental animals were judged to provide *sufficient evidence* for five compounds—AF-2, degraded carrageenan, gyromitrin, Trp-P-1 and Trp-P-2—and *limited* evidence for 2-amino-5-nitrothiazole, cinnamyl anthranilate, nithiazide, ochratoxin A, petasitenine (and flower stalks of *Petasites japonicus* Maxim.), quercetin, senkirkine (and *Tussilago farfara* L.) and zearalenone. The data were *inadequate* to evaluate the carcinogenicity of cholesterol, furazolidone, fusarenon X, kaempferol, nitrovin, symphytine (although there was *limited evidence* for the carcinogenicity of leaves and roots of *Symphytum officinale* L.) and $T_2$-trichothecene. The available data on native (undegraded) carrageenan and agaritine did not provide evidence of carcinogenicity; there was, however, *limited evidence* of the carcinogenicity of derivatives of two fungal metabolites of agaritine.

Epidemiological data were either unavailable or inadequate to evaluate the carcinogenicity to humans of all compounds except cholesterol. The epidemiological data on cholesterol were summarized and evaluated according to the three contexts in which cholesterol has been measured, i.e., in the diet, blood and faeces. Although the Working Group judged that there was *inadequate evidence* from epidemiological studies that cholesterol as such is carcinogenic to humans, there was *limited evidence* to indicate that raised dietary intake of cholesterol is associated with an increased risk of breast and colo-rectal cancer. With respect to serum cholesterol, the findings from cholesterol-lowering intervention studies (reduced dietary-cholesterol intake or drug-induced) indicated no change in cancer risk consequent upon a reduction in serum cholesterol. However, results from observational studies (in which the risk of cancer in individuals in relation to their natural levels of serum cholesterol was ascertained) provided *limited evidence* that male individuals with relatively low concentrations of serum cholesterol have an increased risk of colon cancer; the data pertaining to women and to sites other than the colon were inadequate for evaluation.

Volume 32 is the first in a series of four volumes in which the carcinogenicity of polynuclear aromatic compounds and exposures to complex mixtures in which these compounds are found are evaluated. In this volume, the carcinogenicity to experimental animals and the activity in short-term tests of 48 individual compounds are evaluated; the compounds considered and the evaluations made are shown in Table 4. As these compounds generally occur only within complex mixtures, no epidemiological data on exposure to the individual compounds were available for consideration.

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[26] International Agency for Research on Cancer (1983) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 31, *Some Food Additives, Feed Additives and Naturally Occurring Substances*, Lyon.

[27] International Agency for Research on Cancer (1983) *Ibid.*, Vol. 32, *Polynuclear Aromatic Compounds*, Part 1, *Chemical, Environmental and Experimental Data*, Lyon.

[28] International Agency for Research on Cancer (1984) *Ibid.*, Vol. 33, *Polynuclear Aromatic Compounds*, Part 2, *Carbon Blacks, Mineral Oils and Some Nitroarene Compounds*, Lyon.

Table 4. Compounds considered and evaluations made in Volume 32 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*

| Chemical | Evidence for carcinogenicity in animals | Evidence for activity in short-term tests |
|---|---|---|
| Anthanthrene | limited | inadequate |
| Anthracene | no evidence | no evidence |
| Benz[*a*]acridine | inadequate | inadequate |
| Benz[*c*]acridine | limited | inadequate |
| Benz[*a*]anthracene | sufficient | sufficient |
| Benzo[*b*]fluoranthene | sufficient | inadequate |
| Benzo[*j*]fluoranthene | sufficient | inadequate |
| Benzo[*k*]fluoranthene | sufficient | inadequate |
| Benzo[*ghi*]fluoranthene | inadequate | inadequate |
| Benzo[*a*]fluorene | inadequate | inadequate |
| Benzo[*b*]fluorene | inadequate | inadequate |
| Benzo[*c*]fluorene | inadequate | inadequate |
| Benzo[*ghi*]perylene | inadequate | inadequate |
| Benzo[*c*]phenanthrene | inadequate | inadequate |
| Benzo[*a*]pyrene | sufficient | sufficient |
| Benzo[*e*]pyrene | inadequate | limited |
| Carbazole | limited | inadequate |
| Chrysene | limited | limited |
| Coronene | inadequate | inadequate |
| Cyclopenta[*cd*]pyrene | limited | sufficent |
| Dibenz[*a,h*]acridine | sufficient | inadequate |
| Dibenz[*a,j*]acridine | sufficient | inadequate |
| Dibenz[*a,c*]anthracene | limited | sufficient |
| Dibenz[*a,h*]anthracene | sufficient | sufficient |
| Dibenz[*a,j*]anthracene | limited | inadequate |
| Dibenzo[*c,g*]carbazole | sufficient | inadequate |
| Dibenzo[*a,e*]fluoranthene | limited | no data |
| Dibenzo[*a,e*]pyrene | sufficient | inadequate |
| Dibenzo[*a,h*]pyrene | sufficient | inadequate |
| Dibenzo[*a,i*]pyrene | sufficient | inadequate |
| Dibenzo[*a,l*]pyrene | sufficient | no data |
| 1,4-Dimethylphenanthrene | inadequate | limited |
| Fluoranthene | no evidence | limited |
| Fluorene | inadequate | inadequate |
| Indeno[1,2,3-*cd*]pyrene | sufficient | inadequate |
| 1-Methylchrysene | inadequate | inadequate |
| 2-, 3-, 4- and 6-Methylchrysenes | limited | inadequate |
| 5-Methylchrysene | sufficient | limited |
| 2-Methylfluoranthene | limited | inadequate |
| 3-Methylfluoranthene | inadequate | inadequate |
| 1-Methylphenanthrene | inadequate | sufficient |
| Perylene | inadequate | inadequate |
| Phenanthrene | inadequate | limited |
| Pyrene | no evidence | limited |
| Triphenylene | inadequate | inadequate |

Carbon blacks, mineral oils (lubricant base oils and derived products) and some nitrated polynuclear compounds were evaluated in Volume 33 of the *Monographs*, the second volume in the series on polynuclear aromatic hydrocarbons. Evaluations were made of the carcinogenicity of both carbon black particles and solvent extracts of carbon blacks. The available data were judged *inadequate* to evaluate the carcinogenicity of carbon black particles to experimental animals; there was, however, *sufficient evidence* that solvent (benzene) extracts of most of the carbon blacks tested

are carcinogenic. The epidemiological data provided *inadequate evidence* of carcinogenicity of carbon blacks to humans.

In considering mineral oils, the Working Group divided these petroleum-derived materials and the products derived from them into seven classes, generally on the basis of increasing severity of processing or refinement. These classes and the evaluations of their carcinogenicity to experimental animals are as follows: class 1, vacuum distillates: *sufficient evidence;* class 2, acid-treated oils: *sufficient evidence*; class 3, solvent-refined oils (raffinates): *sufficient evidence* for the carcinogenicity of mildly solvent-refined oils and *no evidence* that severely solvent-refined oils are carcinogenic; class 4, hydro-treated oils: *sufficient evidence* for the carcinogenicity of mildly hydro-treated oils and *inadequate evidence* for that of severely hydro-treated oils; class 5, white oils and petrolatums suitable for food and/or medicinal use: *no evidence* that white oils, when administered by routes other than intraperitoneal injection, are carcinogenic; class 6, aromatic oils, including solvent extracts and catalytically cracked oils: *sufficient evidence*; and class 7, miscellaneous materials, including formulated products and used oils: *inadequate evidence* to evaluate their carcinogenicity as a class but *sufficient evidence* for the carcinogenicity of one sample of used gasoline engine oil and *limited evidence* for that of some cutting oils. The epidemiological data provided *sufficient evidence* that mineral oils (containing various additives and impurities) that have been used in occupations such as mulespinning, metal machining and jute processing are carcinogenic to humans.

Six nitroarenes were also evaluated. Since, in general, humans are not exposed to these compounds individually, no epidemiological data were available. The data from carcinogenicity studies in experimental animals were judged to provide *limited evidence* for the carcinogenicity of 1-nitropyrene and *inadequate evidence* for that of 6-nitrobenzo[*a*]pyrene, 3-nitrofluoranthene and 6-nitrochrysene. There was *limited evidence* that 6-nitrochrysene is active as an initiator in mouse skin carcinogenesis. No data were available to evaluate the carcinogenicity of 1,8-dinitropyrene and 9-nitroanthracene.

(*i*) *Occupational cancer review* (Dr L. Simonato, Dr R. Saracci and Mrs J. Lavallée-Hawken)

The systematic collection of published studies investigating carcinogenic risks in the occupational environment has been continued, using a computerized system for bibliography. A selection of the review in its present state has been published by the International Labour Office in Geneva[29].

(*j*) *Use of job histories in case-control studies to detect occupational carcinogens* (Dr A. Walker and Dr R. Saracci)

A variety of methods has been developed over the past decade for relating work histories to chemical exposures. The Agency is in the process of organizing a conference of the principal developers and users of job-exposure matrices, job-exposure indices, in-depth anamnesis, and job title reviews, in order to develop a consensus with regard to effective methodology. In a related project, we have initiated a study to simplify job classification schemes, using formal clustering algorithms to group job titles in terms of similarity of exposures[30].

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[29] International Labour Office (1983) *Occupational Health and Safety*, Vol. 1, Geneva, pp. 369–375.
[30] Hsieh, C. C., Walker, A. M. & Hoar, S. K. (1983) *Am. J. Epidemiol.*, 117, 575–589.

## 3. SITE-ORIENTED STUDIES

### (*a*) *Etiological studies on liver cancer*

(i) *Aflatoxin and hepatitis B studies in Swaziland* (Dr N. Muñoz and Dr F. G. Peers, Mbabane, Swaziland; UNEP/IARC Contract FP/0107.78-03 (1391)

The primary objective of this study is to assess the impact of a rural development programme on the level of aflatoxin contamination of foodstuffs in Swaziland and to determine the prevalence of the several markers of hepatitis B virus infection in the same population. The main activities implemented during the last year can be summarized as follows:

(1) *Cancer registration.* Up to March 1983, about 600 cases of cancer had been registered. The crude rate for all cancers was about 30 per 100 000, a rate much lower than those reported from other African registries. Of the 600 cancer cases, 60 were liver cancer, 40 of which were confirmed after a review of clinical records. The diagnosis was confirmed in 28 of these cases by histology and in the remainder by α-fetoprotein tests. The distribution of the 40 primary liver cancer cases by topographical region shows higher rates in the low veld region of Swaziland.

(2) *Aflatoxin analysis of crops.* A total of about 3000 crop samples derived from agricultural surveys conducted by the Central Statistics Office, the grain storage section and the Food and Agriculture Organization project on the prevention of food losses have been collected and are being analysed for aflatoxin levels in the Agency laboratories. Additionally, some 2000 crop and other samples have been received from agronomy trials and from commercial food and feed. Up to the end of January 1983, a total of 3816 samples had been analysed, and 204 (5.3%) were positive for aflatoxin. The distribution of the positive samples by topographical region is shown in Table 5.

Table 5. Distribution of aflatoxin-positive crop samples by topographical region of Swaziland

| | High veld | Middle veld | Low veld | Lubombo | Total |
|---|---|---|---|---|---|
| Total no. collected | 981 | 1669 | 925 | 241 | 3816 |
| Total no. positive | 27 | 81 | 77 | 19 | 204 |
| Percentage | 2.7 | 4.8 | 8.3 | 7.9 | 5.3 |

A dietary survey of aflatoxin contamination was conducted from July 1982 to June 1983. A similar sampling system to that used in the 1972 survey was used, except that four *ndunas* were chosen rather than two in each of the 11 arable areas. 'Man-sized' portions of a main meal and of sauce were collected separately and each was weighed before samples were taken for analysis. At the same time, samples of snack foods were taken from each household. Up to January 1983, 1329 diet and snack food samples had been analysed for aflatoxin; the distribution of positive samples by topographical region is shown in Table 6.

(3) *Hepatitis B virus studies.* A total of 3047 serum samples have been collected through the blood bank in Swaziland, mainly from subjects aged between 16–45 years. All have been tested for hepatitis B virus markers; preliminary results are shown in Table 7. The high prevalence of hepatitis B surface antigen carriers among males in the Swaziland is striking; the possibility of a trend to a higher proportion of carriers in the low veld and in Lubombo is being investigated.

Table 6. Distribution of aflatoxin-positive diet and snack food samples by topographical region in Swaziland

| | High veld | Middle veld | Low veld | Lubombo | Total |
|---|---|---|---|---|---|
| Total no. analysed | 404 | 344 | 349 | 234 | 1331 |
| Total no. positive | 15 | 21 | 17 | 5 | 58 |
| Percentage | 3.7 | 6.1 | 4.9 | 2.1 | 4.4 |

Table 7. Hepatitis B virus markers in Swaziland

| Topographical area | No. subjects tested | | Hepatitis B virus-exposed | | | | Hepatitis B surface antigen carriers | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | Females | Males | | Females | | Males | | Females | |
| | | | No. | % | No. | % | No. | % | No. | % |
| High veld | 569 | 517 | 488 | 85.8 | 397 | 76.8 | 118 | 20.7 | 78 | 15.1 |
| Middle veld | 698 | 619 | 598 | 85.7 | 454 | 73.3 | 151 | 21.6 | 82 | 13.2 |
| Low veld | 261 | 225 | 231 | 88.5 | 187 | 83.1 | 72 | 27.6 | 38 | 16.9 |
| Lubombo | 96 | 62 | 87 | 90.6 | 47 | 75.8 | 27 | 28.1 | 13 | 21.0 |
| Total | 1624 | 1423 | 1404 | 86.5 | 1085 | 76.2 | 368 | 22.7 | 211 | 14.8 |

In addition, finger-prick blood samples were collected from 400 children aged 6-16 years during a schistosomiasis survey carried out by USAID. These samples have also been tested for hepatitis B viral markers.

A case-control study is being conducted on 22 cases of primary liver cancer and 22 controls matched by sex and age. Thirteen cases and two controls were found to be positive for hepatitis B surface antigen—a relative risk of 14; 95% confidence intervals, 2.34–147.50.

(4) *Miscellaneous studies.* Four-hundred urine specimens were collected from the same children participating in the schistosomiasis survey and are being stored in a freezer until an appropriate test becomes available to test them for the presence of aflatoxin metabolites.

During March 1983, an evaluation mission was sent to Swaziland at the request of the United Nations Development Programme to make recommendations on the future of this project. The mission was composed of Dr A. Linsell, former Agency staff member, Dr F. X. Bosch, Agency consultant, Mr K. Saita, Director of Administration and Finance, the Agency, and Mr P. Smith, London School of Hygiene and Tropical Medicine, London. It was decided to terminate the project, as planned, in September 1983 and to continue support to the cancer registry as a separate activity.

(ii) *Cohort study on hepatitis B virus and liver cancer* (Dr N. Muñoz; in collaboration with Professor Phoon Wai-On, Dr Fong Ngon Phoon and Mr Wong Ah Fook (Department of Social Medicine and Public Health, University of Singapore, DEB/79/021)

A total of 5515 subjects had been admitted to this cohort up to May 1983, 4775 of whom have been tested for the various markers of hepatitis B virus (Table 8).

Table 8. Cohort study on hepatitis B virus and liver cancer

| Source | No. tested | Positive for hepatitis B surface antigen | |
|---|---|---|---|
| | | No. | % |
| Hospitals | 3160 | 436 | 13.8 |
| Blood transfusion service | 1085 | 26 | 2.4 |
| Singapore Anti-Tuberculosis Association | 214 | 21 | 9.8 |
| Private practitioners | 205 | 18 | 8.8 |
| Singapore Action Group for the Elderly | 47 | 4 | 8.5 |
| Others | 64 | 5 | 7.8 |
| Total | 4775 | 510 | 10.7 |

(iii) *Hepatitis B virus, aflatoxin and liver cancer in the Philippines* (Dr N. Muñoz: in collaboration with Dr E. Domingo, Dr A. Lingao, Dr M. Abrigo and Dr N. Torres, Department of Internal Medicine, Philippines General Hospital, Manila; Dr J. Bulatao-Jayme, Food and Nutrition Research Institute, Manila; and the WHO Regional Office for the Western Pacific, Manila, DEB/81/011)

(1) *Perinatal transmission of hepatitis B virus*: A total of 1386 mother/cord blood pairs were collected at the Fabella Memorial Hospital, Manila, from March 1981 to March 1982. At least one follow-up serum sample was collected from 312 babies during the first 18 months of life up to May 1983, and for 277 of them enough serum was available to test for the various markers of hepatitis B surface antigen. Table 9 summarizes these findings according to the hepatitis B virus status of the mother.

Table 9. Mother-to-infant transmission of hepatitis B virus (HBV) in the Philippines (277 mother/cord blood pairs)

| Mother's HBV status | No. | % | Infants | | | |
|---|---|---|---|---|---|---|
| | | | HBV-exposed | | HBsAg+ | |
| | | | No. | % | No. | % |
| HBsAg+ | 29 | 10.5 | 8 | 27.6 | 7 | 24.1 |
| HBcAb+ | 34 | 12.3 | 0 | – | 0 | – |
| HBcAb+, HBsAb+ | 94 | 33.9 | 0 | – | 0 | – |
| HBsAb+ | 3 | 1.1 | 2 | 66.6 | 1 | 33.3 |
| HBV(–) | 117 | 42.2 | 0 | – | 0 | – |

HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody

(2) *Case-control study of parents of patients with liver cancer and of parents of control patients*: Blood specimens have been collected from both parents and siblings of 20 patients with liver cancer and from parents and siblings of 10 control patients. Two controls, matched by sex and age, are being included for each case—one irrespective of serological status and the second an asymptomatic hepatitis B surface antigen carrier. The preliminary analysis of the first ten triplets (one case and two controls) shows no significant difference between cases and controls.

(iv) *Intervention studies using hepatitis B virus vaccine*

(1) *Intervention study in Singapore* (Dr N. Muñoz and Dr N. Day; in collaboration with Professor Oon Chong Jin, Professor Chan Soh-Ha, Dr Ewe Hui Sng and Dr Lily Chan, University of Singapore, Singapore; DEB/83/002)

The Singapore Government has approved a programme for the control of HBV, aimed at reducing the incidence of acute and chronic liver disease by vaccination of the following high-risk groups: children born to hepatitis B surface antigen (HBsAg)-positive mothers, hospital personnel and contacts of HBsAg-positive individuals. This programme is expected to start in 1984. In order to measure the impact of this vaccination programme on liver cancer incidence, an unvaccinated control group must be available. The Government of Singapore has agreed to the use of a temporal or historical control group, which will be composed of 35 000 live births occurring during the year prior to the beginning of vaccination.

The collection of prenatal sera started on 9 March 1983, and 4800 specimens had been collected up to 31 May 1983. These sera are being tested for all HBV markers. A registry of the 35 000 babies born before the vaccination starts will be established, as well as a registry of all vaccinated subjects. The occurrence of liver cancer in both groups will be determined four to five decades later by linkage in the cancer registry.

(2) *Intervention study in The Gambia* (Dr N. Muñoz, Dr G. O'Conor, Dr N. E. Day and Dr M. Parkin)

Ad-hoc working groups composed of Agency staff members and international experts on HBV were convened in Lyon on 27–28 January 1983 and in Geneva on 4 February 1983 to discuss the feasibility of carrying out an intervention study to evaluate the effectiveness of the HBV vaccine for the prevention of liver cancer in The Gambia. It was concluded that in Africa The Gambia probably offers the optimal conditions for carrying out such a study. Dr R. Ryder, from the Medical Research Council Laboratories in The Gambia, who initiated this idea, was invited as a consultant to the Agency from 18 April to 6 May to write the first draft proposal for the study. A final draft is now being prepared. Since the implementation of this proposal will involve a substantial financial commitment, a number of sources of support are being considered.

The proposed study represents a unique opportunity for conducting the first large HBV vaccine intervention trial specifically designed to provide statistically valid conclusions related to the efficiency of vaccination for the prevention of chronic liver disease and hepatocellular carcinoma in a high-risk population. The study design will also permit the generation of new information on the natural history of hepatitis B in West Africa and determination of the duration of HBV vaccine-induced immunity.

(*b*) *Cancers of the gastrointestinal tract*

(i) *Precancerous lesions of the oesophagus in the People's Republic of China* (Dr N. Muñoz, Dr J. Wahrendorf and Dr N. E. Day; in collaboration with Dr Li Bing, Dr Zheng You Hui, Dr Zhang Cai-Yun, Dr Zheng Su-Fang, Dr Lu Shih Hsin and Dr Liu Fu Sheng, Beijing Cancer Institute, Beijing; Dr Yang Wen-Xian, Professor Shen Chiun, Dr Yang Kuan-Re, Dr Qu Song Lang, Dr Quiao Si Je, Henan Medical College and Henan Cancer Institute, Henan, People's Republic of China; Professor M. Crespi and Dr A. Grassi, Regina Elena Institute, Rome; Dr D. Thurnham, Dudley Road Hospital, Clinical Investigation Unit, Birmingham, UK; and Dr M. Hambidge, Medical Center, University of Colorado, Denver, CO, USA)

Nutritional studies in both Iran and the People's Republic of China[31] suggest that deficiencies of riboflavin and possibly vitamin A are associated with precancerous lesions of the oesophagus. Epidemiological surveys in both countries have identified the following lesions as precancerous: chronic oesophagitis, epithelial atrophy and dysplasia. To clarify further these associations, an intervention study is being planned in Huixian, Henan Province, People's Republic of China to determine whether combined treatment with retinol, riboflavin and zinc over a one-year period can reduce the proportion of persons diagnosed with chronic oesophagitis or more severe lesions such as atrophy and dysplasia and increase the proportion diagnosed with a normal oesophagus as compared to a group receiving a placebo.

In Huixian, a county with a high risk for oesophageal cancer (120 per 100 000), 600 individuals aged 35–65 years are being selected from a given commune and will be assigned randomly to two treatment groups. One group will receive once a week vitamin capsules containing 50 000 IU of retinol, 200 mg riboflavin and 50 mg zinc as zinc gluconate. The other group will be given a placebo in identical capsules once a week. The treatment will last for one year; at the end of that period endoscopical examinations will be performed to assess and compare the prevalence of precancerous lesions of the oesophagus in the two treatment groups.

A pilot study was carried out in Ton-Sha-Fun production brigade, Huixian, in May 1983 in 50 individuals to test the questionnaire, and blood samples were taken to obtain background levels of riboflavin, retinol, carotenes and zinc. The levels of riboflavin and β-carotene were even lower than those found in Linxian, another high-incidence area for oesophageal cancer.

(ii) *Precancerous lesions of the oral mucosa and oesophagus in Uzbekistan (USSR)* (Dr D. G. Zaridze; in collaboration with Professor N. N. Trapeznikov, Professor B. K. Poddubni, Dr J. P. Kuvshinov, Dr G. V. Ungiadze. Dr B. I. Poljakov, Professor A. S. Petrova, Dr T. T. Kondratjeva, Dr L. S. Koroleva, Professor N. A. Krajevsky, Dr V. I. Rottenberg and Dr S. I. Parshikova, All Union Cancer Research Centre of the USSR Academy of Medical Sciences, Moscow; Dr M. P. Rosin and Dr H. F. Stich, Environmental Carcinogenesis Unit, British Columbia Cancer Research Center, Vancouver, BC, Canada; and Dr D. Thumham, Dudley Road Hospital, Clinical Investigation Unit, Birmingham, UK)

This exploratory survey is an expansion of a local screening programme in an area with a high incidence of oral cancer and a moderately high incidence of oesophageal cancer (Narpai Region of Samarkand oblast). All 2200 men aged between 55 and 69 years who are residents of the region were invited by letter to attend a medical examination by local nurses. A total of 1643 men who responded were interviewed and underwent oral and oesophageal investigations.

A questionnaire was completed for each subject containing information on socio-demographic characteristics, use of *nass*, cigarette smoking, alcohol consumption, dietary habits, medical

[31] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, pp. 43–44.

history, family history of cancer and symptomatology. In all cases in which oral and oesophageal lesions were discovered, photographs of lesions were taken; material was taken for cytological investigations from oral lesions and for biopsies and cytology from oesophageal mucosa. In addition, oral and oesophageal smears were taken for the micronuclei formation frequency test[32, 33]. Blood was collected from 50% of persons with oral and oesophageal pathology for subsequent analysis of levels of riboflavin, retinol and β-carotene.

Evaluation of the results of this exploratory survey and cytological and histological investigations are in progress. After completion of the analysis the possibility of carrying out a randomized trial for chemoprevention of precancerous lesions of the mouth and oesophagus will be examined.

(iii) *Stomach cancer*

(1) *Cohort study on chronic atrophic gastritis and intestinal metaplasia in Slovenia, Yugoslavia* (Dr N. Muñoz; in collaboration with Dr I. Matko and Dr J. Kmet, Gastroenterology Clinic of the University Clinical Centre of Ljubljana, Yugoslavia)

The detailed analysis described in last year's report[34] is still underway.

(2) *Prevalence of precancerous lesions of the stomach in Jiaoxian, People's Republic of China* (Dr N. Muñoz; in collaboration with Dr Li Bing, Dr Zheng You Hui, Dr Wang Kao Ching and Dr Lu Shin Hsin, Beijing Cancer Institute, Beijing; Dr Chou Hui-Min, Quingdao Medical College, Shandong; Dr Yang Min-Lu, Chang-Wei Medical College, Shandong; and Dr Cao Shou-Wei, Medical Research Institute of Shandong, People's Republic of China)

The prevalence of chronic atrophic gastritis detected in the 251 subjects examined endoscopically in May 1981 is being related to different risk factors, including vitamin deficiencies. The results are being prepared for publication.

(3) *Histological classification of gastric dysplasia* (Dr N. Muñoz; in collaboration with Dr S. Ming, Temple University Medical School, Philadelphia, PA, USA; Professor M. Crespi, Regina Elena Institute, Rome; and Professor G. Zampi, University of Florence, Florence, Italy)

The results of a workshop held in May 1982 have been summarized in a report which has been submitted of publication to *Cancer*.

[32] Stich, H. F. & Rosin, M. P. (1983) In: Stich, H. F., ed., *Carcinogens and Mutagens in the Environment*, Vol. II, Boca Raton, FL, CRC Press (in press).
[33] Stich, H. F., Curtis, J. R. & Parida, B. B. (1982) *Int. J. Cancer*, **30**, 553–559.
[34] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, p. 51.

(c) *In-vivo nitrosation, nutritional deficiencies and precancerous lesions and cancers of the gastrointestinal tract* (Mr H. Ohshima, Dr N. Muñoz, Dr A. Aitio, Miss J. Michelon, Miss M. C. Bourgade, Miss M. Blettner, Dr J. Wahrendorf and Dr H. Bartsch; in collaboration with Professor M. Crespi, Dr V. Cassale and Dr V. Ramazotti, Regina Elena Institute, Rome, DEB/81/019; Dr A. Lehtonen and Dr M. Inberg, Turku University, Finland, DEC/81/006; Dr H. Tulinius and Dr T. A. Jönasson, Icelandic Cancer Registry and Saint-Joseph's Hospital Landakot, Reykjavik, DEC/81/020; Dr Li Ping and Dr Lu Shi Hsin, Cancer Institute, Beijing, DEC/81/001; Professor R. Lambert and Dr Y. Minaire, Edouard Herriot Hospital, Lyon, France, DEB/82/010; Dr C. Walters, British Food Manufacturing Industries Research Association, Leatherhead, UK, DEC/81/004; and Professor S. Kamiyama, Akita University, School of Medicine, Akita, Japan, DEC/83/006)

Endogenous formation of *N*-nitroso compounds has long been suspected to be associated with an increased risk of cancers of the stomach, oesophagus and bladder, but convincing epidemiological evidence is lacking. The general objective of these pilot studies[35] is to collect more data on endogenous nitrosation in human subjects with precancerous lesions of the oesophagus and stomach and in asymptomatic subjects from high- and low-risk areas for cancers of the oesophagus and stomach. Potential in-vivo nitrosation in humans is being estimated by measuring *N*-nitrosamino acids such as *N*-nitrosoproline excreted in 24-h urine[36].

(i) *Precancerous lesions of the oesophagus*

In order to measure individual exposure to *N*-nitroso compounds and their precursor nitrate/nitrite, 24-h urine samples were collected from 238 subjects living in high- (Linxian) and low- (Fanxian) incidence areas for oesophageal cancer in the People's Republic of China, as follows: (A) untreated subjects, (B) subjects who had ingested 100 mg L-proline three times a day after each meal and (C) subjects who had ingested 100 mg proline three times a day with 100 mg vitamin C. These urine samples were analysed for nitrate and for some *N*-nitrosamines such as *N*-nitrosoproline, *N*-nitrososarcosine, *N*-nitrosothiazolidine 4-carboxylic acid and *N*-nitroso-2-methylthiazolidine 4-carboxylic acid. The latter two compounds have recently been identified in human urine (see p. 113: 'Identification of new *N*-nitroso compounds in human urine').

The results of this study are summarized in Table 10. The amounts of nitrate and of each of four *N*-nitrosamino acids excreted in the urine of undosed subjects from Linxian were significantly greater than those excreted by Fanxian subjects. The total amounts of these *N*-nitrosamino acids excreted in the urine by Linxian subjects ranged from trace amounts to 79 μg/day/person with a mean value of 22.5 μg, which was significantly higher ($p < 0.001$) than the mean value of 7.3 μg (range: trace—46) detected in Fanxian subjects. These data suggest that subjects living in the high-incidence area are exposed to higher amounts of nitrate and *N*-nitroso compounds than those living in the low-incidence area.

Figure 3 shows the frequency distribution of the amount of NPRO excreted in the urine of these five study groups. After ingestion of proline, the urinary levels of NPRO in the subjects of each area increased significantly, compared with those of the undosed subjects. However, intake of vitamin C reduced significantly the levels of *N*-nitrosamino acids, including NPRO (Table 10).

[35] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, p. 48.
[36] Ohshima, H. & Bartsch, H. (1981) *Cancer Res.*, **41**, 3658-3662.

Table 10. The amount (median) of *N*-nitrosamino acids[a] and nitrate excreted in 24-h urine of subjects living in Linxian and Fanxian counties in northern China

| Area and protocol | No. of subjects | NSAR µg/day per person | NPRO | NTCA | NMTCA | Total | Nitrate mg/day per person |
|---|---|---|---|---|---|---|---|
| *Linxian* | | | | | | | |
| Control (LA) | 44 | 0.27 | 5.48 | 9.83 | 0.6 | 16.18 | 95 |
| Proline (LB) | 50 | 0.19 | 8.18 | 7.67 | 0.3[b] | 16.34 | 85 |
| Proline/Vitamin C (LC) | 48 | 0.1 | 2.23 | 2.15 | 0.3[b] | 4.78 | 89 |
| *Fanxian* | | | | | | | |
| Control (FA) | 40 | 0.1 | 1.69 | 1.27 | 0.3[b] | 3.36 | 48 |
| Proline (FB) | 56 | 0.17 | 4.07 | 2.04 | 0.3[b] | 6.58 | 57 |
| p values of comparisons | | | | | | | |
| LA-FA | | 0.017 | <0.001 | <0.001 | NS | <0.001 | <0.001 |
| LB-FB | | NS | <0.002 | <0.001 | 0.02 | <0.001 | <0.006 |
| LC-LA | | NS | <0.001 | <0.001 | <0.001 | <0.001 | NS |
| LC-LB | | NS | <0.001 | <0.001 | 0.01 | <0.001 | NS |

[a] NSAR, *N*-nitrosarcosine; NPRO, *N*-nitrosoproline; NTCA, *N*-nitrosothiazolidine 4-carboxylic acid; NMTCA, *N*-nitroso-2-methylthiazolidine 4-carboxylic acid
[b] Limit of detection
NS, not significant

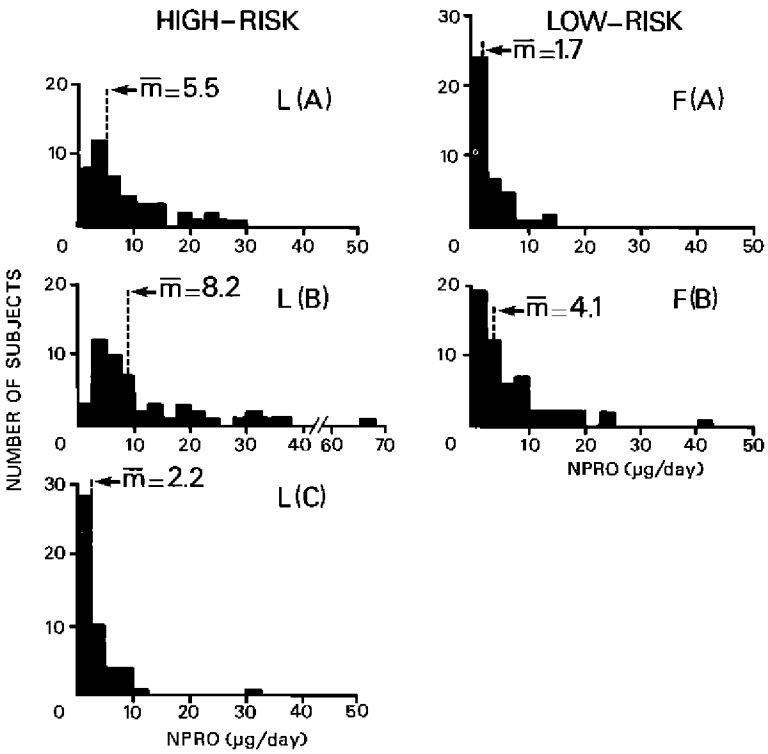


Figure 3. Urinary excretion of *N*-nitrosoproline by subjects in high- and low-incidence areas of oesophageal cancer in northern People's Republic of China; L, Linxian (high-risk); F, Fanxian (low-risk); A, undosed; B, proline; C, proline + vitamin C

These results indicate that a further increase in endogenous formation of *N*-nitroso compounds may occur when amine precursors are present in the stomach and that this can be effectively blocked by intake of vitamin C.

Similar studies are being planned in the same counties in northern China but in different seasons, and also in different areas in northern China with a high risk of oesophageal cancer.

(ii) *Precancerous lesions of the stomach*

Subjects included in these studies are: (1) patients with chronic atrophic gastritis, with and without intestinal metaplasia; (2) patients with pernicious anaemia; (3) people who have undergone partial gastrectomy (Billroth II); and (4) cimetidine-treated patients. The common denom-

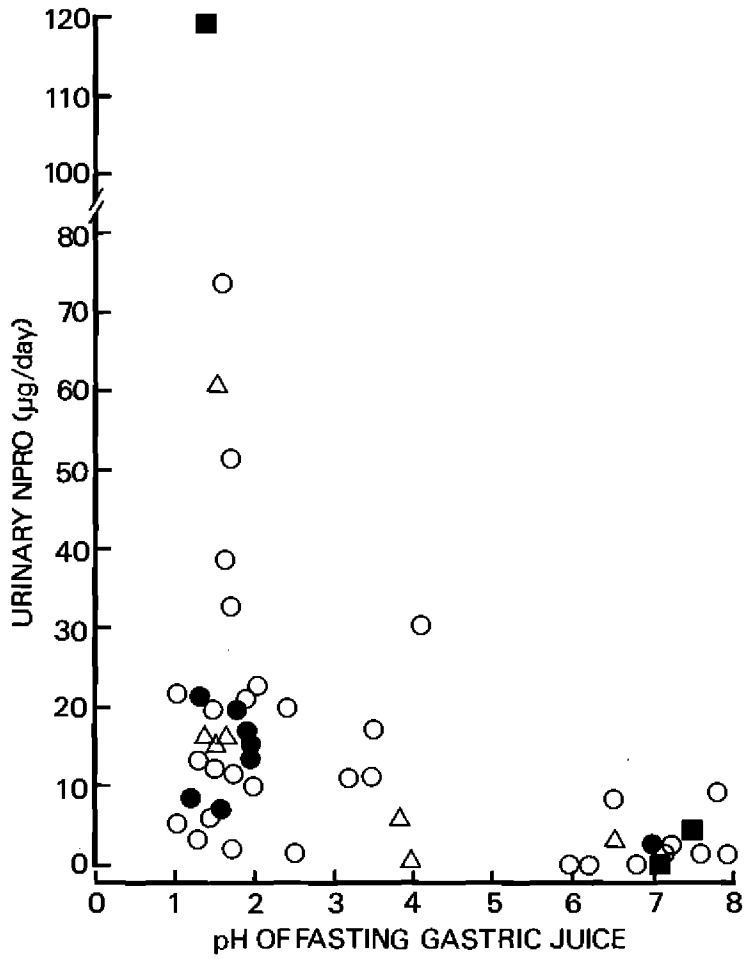


Fig. 4A. Excretion of *N*-nitrosoproline (NPRO) in the urine of fasting subjects in relation to the pH of their gastric juice; ●, normal mucosa (n = 8); △, superficial gastritis (n = 7); ○, chronic atrophic gastritis (n = 31); ■, dysplasia (n = 3)

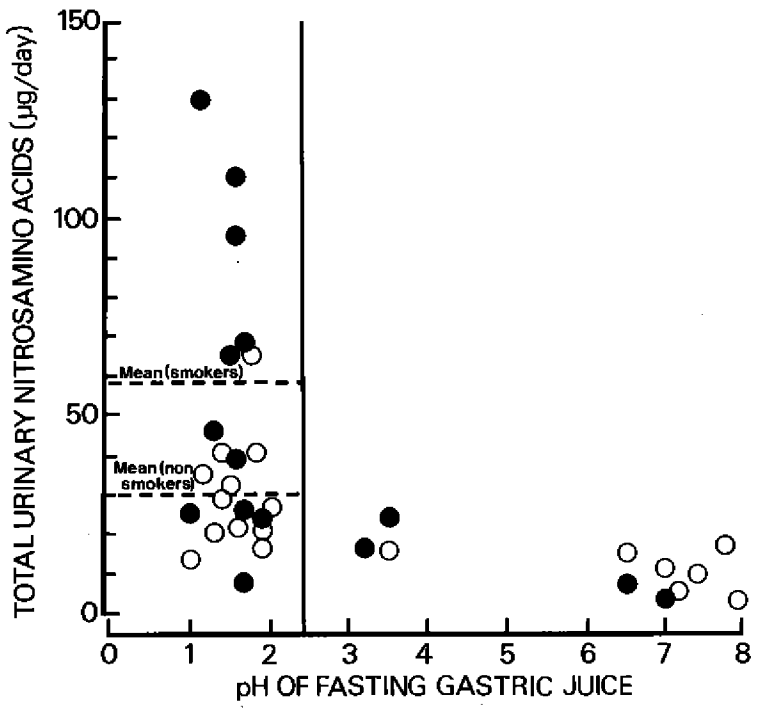


Fig. 4B. Total urinary *N*-nitrosamino acids in the urine of fasting subjects in relation to the pH of their gastric juice; ●, smokers (n = 11); ○, non-smokers (n = 12)

inator for all of these subjects is an achlorhydric stomach, which may provide a suitable milieu for intragastric formation of *N*-nitroso compounds due to the presence of a large number of the bacteria that may be involved in the conversion of nitrate to nitrite and subsequent nitrosation in the stomach.

The following procedures are being included in the protocol for each study subject[37]: (1) completion of a questionnaire, (2) gastroscopy, (3) collection of fasting gastric juice (the pH, bacterial count and the amount of total *N*-nitroso compounds are being measured), (4) histopathological evaluation of biopsy samples, (5) the *N*-nitrosoproline (NPRO) test.

Some interim results are now available on study subjects with and without atrophic gastritis: in Figure 4A, the levels of NPRO excreted in the urine of subjects who ingested 260 mg nitrate in beetroot juice and then 500 mg L-proline are plotted against the pH of their gastric juice. The yield of NPRO in the urine of these subjects ranged from trace amounts to 120 mg/day per person. Similarly, the total amounts of four *N*-nitrosamino acids (NPRO, *N*-nitrososarcosine, *N*-nitrosothiazolidine 4-carboxylic acid and *N*-nitroso 2-methylthiazolidine 4-carboxylic acid; see p. 113) excreted by the subjects are plotted against the pH of fasting gastric juice (Fig. 4B). Although final

[37] Bartsch, H., Ohshima, H., Muñoz, N., Crespi, M. & Lu, S. H. (1983) In: Harris, C. C. & Autrup, H. N., eds, *Human Carcinogenesis* (in press).

confirmation is still needed, subjects who smoke cigarettes appeared to produce more NPRO and other nitrosamino acids than non-smokers.

A comparison of endogenous nitrosation in subjects with and without precancerous conditions of the stomach is pending until all histological evaluations, the levels of total nitroso compounds and bacteria counts in fasting gastric juice become available.

In 1983, a new pilot study was initiated in the northern part of Japan in collaboration with Professor Kamiyama. About 300 samples of 24-h urine were collected from 100 subjects living in high- (Akita) and low- (Iwate) incidence areas for stomach cancer. Three different urine samples were collected from each subject: (1) undosed, (2) after ingestion of 100 mg L-proline three times a day after each meal and (3) after ingestion of 100 mg proline three times a day together with 100 mg vitamin C. Analyses for nitrate, nitrite and *N*-nitroso compounds are under way. Furthermore, a blood sample was collected from each subject to determine the levels of vitamins (A, $B_2$, C and E) and trace elements (Se and Zn) as an index of nutritional status.

(*d*) *Cancers of the pancreas, gall-bladder and bile duct* (Dr A. Walker, Dr R. Saracci and Dr J. Wahrendorf; in collaboration with Dr A. B. Miller, National Cancer Institute, Toronto, Canada; Dr A. S. McMichael, CSIRO, Adelaide, Australia; Dr F. de Waard, Royal Institute for Public Health, Utrecht, The Netherlands; and Dr W. Zatonski, Institute of Oncology, Warsaw)

The rising incidence of cancer of the pancreas, the high fatality rate associated with the disease, and the emergence of new biological information from studies of animal models have prompted the collaborators in the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) programme to initiate a multi-centre case-control study of cancer of the pancreas. Specific hypotheses to be addressed are: (1) that fats from animal sources carry risks that are identifiably different from those associated with fats from vegetable sources; (2) that exposure to stimulants of cholecystokinin release increases risk for pancreatic cancers; (3) that the timing and variability of food and alcohol consumption are risk factors for the disease, over and above the simple effects of total quantity of exposure; and (4) that pancreatic cancer is associated with endocrinopathies other than diabetes. In addition, data will be collected to assess the effects of known risk factors, such as smoking, and recent etiological candidates such as coffee consumption. Cancers of the bile duct and gall-bladder will be included in the same protocol on an exploratory basis.

Principal collaborators met in April 1983 to plan the master protocol and develop pilot studies. Several methodological issues are being addressed in the pilot phase: first, it is apparent that a single dietary questionnaire cannot be adapted effectively to the needs of all participating centres. It was suggested that comparable case-control comparisons for each area could be obtained by the use of local questionnaires developed on the basis of common principles. Second, a major impediment in studies of pancreatic cancer is the fact that few interviews can be conducted because of the very poor prognosis of the disease. The questions of what kinds of proxy interviews are feasible—who can be interviewed, what questions can be asked, and how would case and control proxies differ systematically in their responses—are being addressed in a series of studies in the participating centres, which will form the basis of the definitive data collection procedures beginning in 1984.

(*e*) *Dutch-Japanese case-control study of prostatic cancer* (Dr D. G. Zaridze; in collaboration with Professor F. H. Schröder, Dr F. J. W. ten Kate and Dr F. H. de Jong, Erasmus University, Rotterdam, The Netherlands, DEB/81/042; Dr R. Hayes, Study Centre of Social Oncology, Dutch Cancer Foundation, Rotterdam, The Netherlands; Professor O. Yoshida, Professor K. Okada, Dr K. Oishi and Dr H. Yamabe, Kyoto University, Kyoto, Japan; and Dr Y. Ohno, Nagoya University, Nagoya, Japan)

The collection of material for this study started in 1982 and has been continued in 1983. In Kyoto, about 100 patients with cancer, 300 patients with benign prostatic hyperplasia and 100 general medical controls matched individually with cancer patients have been enrolled in the study.

In Rotterdam, where data collection began in November 1982, 30 cases of cancer, 30 cases of benign prostatic hyperplasia and 30 general medical controls matched individually with cancer cases have been collected. All persons enrolled in the study, both in Japan and in The Netherlands, have been interviewed; blood samples have been taken and stored for analysis of testosterone (total and free fraction), dihydrotestosterone, oestradiol, serum hormone binding globulin and vitamins (retinol and β-carotene). The collection of material will continue in 1984–1985.

At a working group meeting held in Kyoto (14–16 December 1982), the reports from the individual centres were discussed. In addition, the results of two pilot studies were presented:

(1) The study carried out by the Rotterdam group comparing the retrospective dietary history questionnaire technique (as used in this study) with data collected by the seven-day record method showed that the two methods produce comparable results, with correlation coefficients of about 0.60 for nutrients such as total fat, saturated and polyunsaturated fat and cholesterol.

(2) The pilot study on possible variations in blood testosterone levels with regard to time of sampling (before admission, day of admission, day before surgery) and to study place (Rotterdam or Kyoto) showed no difference in blood testosterone levels in relation to time of sampling, whereas statistically significant differences were noted in testosterone levels between the Rotterdam and Kyoto blood samples.

(*f*) *Descriptive epidemiology of selected sites of cancer*

This element of the descriptive epidemiology programme draws together information about various cancer sites and seeks to uncover new facets of their behaviour and distribution, to give insight into possible etiology.

(i) *Childhood cancer* (Dr C. S. Muir and Dr D. M. Parkin)

The incidence of cancer in childhood is fairly constant around the world and, for most sites, varies by a factor of around two, in contrast to cancers that occur at a later age. Clues to etiology are few. Published incidence data on childhood cancer are difficult to interpret, since such cancers are usually classified only by site, whereas the tumour morphology is of great importance in childhood neoplasms. An informal exploratory meeting on childhood cancer was convened by the Agency in Seattle in September 1982. Those present (Dr P. Boyle, Glasgow, UK; Dr N. E. Breslow, Seattle, WA, USA; Dr G. J. Draper, Oxford, UK; Professor R. Flamant, Villejuif, France; Professor T. Hirayama, Tokyo, Japan; Dr M. McC. Curnen, Hartford, CN, USA; Dr C. S. Muir, Lyon, France; Dr D. M. Parkin, Lyon, France; Dr J. A. H. Waterhouse, Birmingham, UK; Dr J. L. Young, Bethesda, MD, USA) decided that the collection of international data by sex, single year of age and histology was the major priority and that the work should be centralized at the Agency.

(ii) *Malignant melanoma* (Dr C. S. Muir and Mrs J. Nectoux; in collaboration with Dr E. van Esch, The Netherlands Cancer Institute, Amsterdam, DEB/83/005)

*Detailed topographical distribution of malignant melanoma:* The incidence of cutaneous malignant melanoma continues to rise in fair-skinned people at a rate of some 5 to 7 percent *per annum*. Thirty-five cancer registries are collaborating in a study established to define more precisely the topographical distribution of cutaneous malignant melanoma in various parts of the world and to ascertain whether the patterns are consistent with the hypothesis that it is associated with solar radiation. Information on the much rarer ocular and visceral malignant melanomas was also requested to investigate whether there is any evidence for the existence of a circulating factor. Most of the promised data have now reached the Agency.

*Change in diagnostic criteria for pigmented skin lesions:* Seventeen pathological laboratories, mainly in Europe and Australia, have agreed in principle to participate in a study, the purpose of which is to evaluate whether at least part of the increase in the incidence of cutaneous malignant melanoma observed over time could be due to changes in diagnostic criteria. The study design calls for reassessment of diagnoses of benign pigmented skin lesions and of cutaneous malignant melanoma for 1930, 1955 and 1980. Whereas such material will be readily available for 1955 and 1980, that for 1930 will not always be sufficient. Two laboratories are, however, likely to meet the full requirements of the study.

(iii) *Cancer of the larynx* (in collaboration with Dr S. Schraub, Regional Hospital Centre, Besançon, France; and Dr P. Schaffer, Department of Hygiene, Faculty of Medicine, Louis Pasteur University, Strasbourg, France)

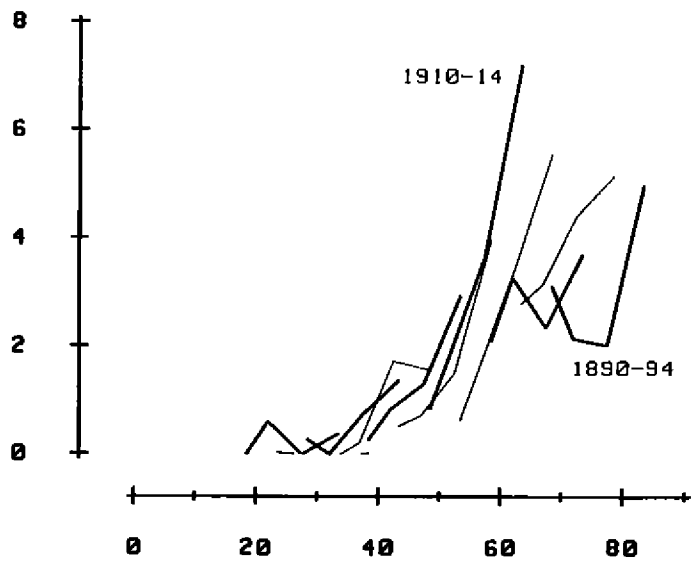


Fig. 5. Incidence of laryngeal cancer in women in Liverpool, UK, by birth cohort. Despite the small numbers, which give rise to statistical instability, it can be seen that on attaining a given age incidence in successive birth cohorts is higher.

Table 11. Incidence rates and sex ratios around 1975 for cancers of the head and neck, oesophagus and lung in the departments of Bas-Rhin and Doubs, France. Comparisons with Bombay, India and Birmingham, UK

| ICD No. 8th Rev. | Bas-Rhin | | | Doubs | | | Bombay | | | Birmingham | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | M/F | M | F | M/F | M | F | M/F | M | F | M/F |
| (a) 141 Tongue | 7.4 | 0.7 | 11 | 7.9 | 0.5 | 16 | 10.2 | 4.1 | 2 | 0.8 | 0.5 | 2 |
| (b) 143–5 Oral cavity | 9.6 | 0.8 | 12 | 6.2 | 0.4 | 16 | 5.0 | 5.1 | 1 | 1.4 | 0.6 | 2 |
| (c) 145 Oropharynx | 11.6 | 0.8 | 15 | 7.0 | 0.6 | 12 | 4.7 | 1.3 | 4 | 0.7 | 0.2 | 4 |
| (d) 147 Hypopharynx | 10.2 | 0.2 | 51 | 10.0 | 0.1 | 100 | 8.0 | 2.2 | 4 | 0.7 | 0.6 | 1 |
| (e) 161 Larynx | 11.2 | 0.1 | 100 | 13.3 | 0.5 | 26 | 12.9 | 2.6 | 5 | 4.0 | 0.5 | 8 |
| (f) 162 Lung | 54.3 | 4.2 | 13 | 58.9 | 2.6 | 23 | 15.7 | 10.7 | 1 | 79.9 | 13.7 | 6 |
| (g) 150 Oesophagus | 17.0 | 0.8 | 21 | 13.0 | 0.7 | 19 | 14.2 | 4.0 | 4 | 5.5 | 2.9 | 2 |
| (h) 140–209 All sites | 305.0 | 196.3 | 1.6 | 298.0 | 182.5 | 1.3 | 140.5 | 128.5 | 1.1 | 246.9 | 193.6 | 1.3 |
| a-e/h% | 16.4% | 1.3% | – | 14.9% | 1.2% | – | 29.0% | 11.9% | – | 3.1% | 1.2% | – |
| g/h% | 5.6% | 0.4% | – | 4.4% | 0.4% | – | 10.1% | 3.1% | – | 2.2% | 1.5% | – |

The Agency has a long-standing interest in laryngeal cancer[38], a disease which exhibits wide international variation in incidence and from which mortality is still increasing in some countries, e.g. France, and falling in most others. Although it is rare in women, a rise is nonetheless discernible in birth cohorts (Fig. 5). Analysis of recently published data from the Departments of Doubs and Bas-Rhin, France (Table 11) has shown extraordinarily high levels of oral-laryngeal-pharyngeal cancer, with intriguing differences between the two departments.

Data analyses by Dr V. Guinee (M. D. Anderson Hospital, Houston, TX, USA), Coordinator of the International Cancer Patient Data System (ICPDS) under the aegis of the Committee for International Collaborative Activities of the International Union Against Cancer, and by Dr C. Gillis (The West of Scotland Cancer Registry, Glasgow, UK) have revealed international differences in the anatomical distribution of cancer within the larynx. Plans are hence being drafted for an international descriptive study of these neoplasms.

(iv) *Cancer of the pancreas* (Dr A. Walker)

The incidence of pancreatic cancer has been examined in relation to that of other cancers which are 'markers' of exposure to a variety of agents or which have been found in association with pancreatic cancer in studies of case series. For this purpose, data were abstracted from the Agency's base on cancer incidence for countries and regions in which there are several registries that contain a minimum of 50 cases of each cancer studied. The already well-established relationship between cancer of the pancreas and smoking was borne out as a correlation between the incidences of cancers of the bronchus/trachea and the pancreas within regions. An examination of the relationship between laryngeal and pancreatic cancer, conditional on rates for bronchial/tracheal cancer, suggested a further contributory effect of alcohol consumption. The phenomenon observed in autopsy series, that multiple endocrine cancers can accompany cancer of the pancreas, was not confirmed in the incidence data in the form of correlations among endocrine and pancreatic cancer incidences. This suggests that the phenomenon of multiple endocrine primary cancers being associated with pancreatic cancer is the result of a single process which generates the various cancers, rather than of the independent action of common exogenous causes on the various target organs.

## 4. NUTRITION AND CANCER

(*a*) *Case-control study of adenomatous polyps of the large bowel* (Dr D. G. Zaridze; in collaboration with Professor M. Crespi, Regina Elena Institute, Rome, DEB/81/040; and Dr M. Hill, Public Health Laboratory Services, Centre for Applied Microbiology and Research, Salisbury, UK, DEB/81/041)

The study plan was described in the *Annual Report 1982*[39]. Progress over the past year has consisted in developing a dietary questionnaire and diary for recording food intake and in piloting the study.

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[38] Tuyns, A. J. (1982) In: Magnus, K. ed., *Trends in Cancer Incidence. Causes and Practical Implications*, Washington DC, Hemisphere, pp. 199-214.

[39] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, p. 63.

(*b*) *Prospective study on diet and related factors in the development of cancer at selected sites* (Dr D. G. Zaridze; in collaboration with Dr E. Trell, Department of Preventive Medicine, Lund University, Malmö, Sweden; Professor N. Sternby, Department of Pathology, Lund University, Malmö, Sweden; Dr J. Cummings and Dr S. Bingham, Medical Research Council, Dunn Clinical Nutrition Centre, Cambridge, UK, DEB/81/038; Dr M. Hill, Public Health Laboratory Service, Centre for Applied Microbiology and Research, UK, DEB/81/037; and Dr D. Thurnham, Clinical Investigation Unit, Dudley Road Hospital, Birmingham, UK)

The study proposal, as outlined in the *Annual Report 1982*[40], underwent a series of discussions in 1983. Consultations have been held with regard to the study design, collection of dietary information and collection and storage of biological material. The feasibility of implementing such a long-term project is being discussed extensively. Pilot studies are tentatively scheduled for 1984.

(*c*) *Cancer of the gastrointestinal tract in Belgium* (Dr A. J. Tuyns; in collaboration with Mrs L. Ravet-Ramioul, Laboratory of Epidemiology, School of Public Health, Brussels, DEB/78/014; and with a group of cardiologists; supported by the Belgian Fund for Scientific Research)

This study stems from a study on mortality from gastric, colonic and rectal cancer, which showed an excess risk for gastric and for rectal cancer in the Flemish part of the country in contrast with the Walloon part. A case-control study was set up as part of a wide investigation on the effects of diet on health (EIAS: Enquête Interuniversitaire sur l'Alimentation et la Santé), of which digestive cancers are one major component and cardiovascular diseases the other.

The cancer investigation is limited to one province in each region. The interviewing of cases has now been terminated, except for oesophageal cancer and for pancreatic cancer. The controls consist of a rectangular population sample, taking into account geographic and urban-rural distribution. The interviewing of this sample has been terminated in the province of Liège and will soon be finished in the province of Oost-Vlaanderen. Validity checks are under way.

The various hypotheses involving food in relation to gastric, colonic and rectal cancer will be studied. These were reviewed in a paper presented in Brussels[41].

(*d*) *Large-bowel cancer in Greece* (Dr N. E. Day and Dr A. Tzonou; in collaboration with Professor D. Trichopoulos, Department of Hygiene and Epidemiology, School of Medicine, Athens)

This study was designed to assess the role of diet in the etiology of large-bowel cancer. Since the incidence of large-bowel cancer in Greece is low, although increasing, and since the diet of the Athens population is varied and changing, a picture different from that observed in North America and western Europe was anticipated. The results indicated a strong protective effect of green vegetables and increases in risk associated with high meat consumption (relative to the mean levels in Athens). When these two dietary components are combined into a dietary score, a large variation

[40] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, p. 64.
[41] Tuyns, A. J. (1982) *Acta gastroenterol. Belg.*, **45**, 146–157.

in risk is seen (Table 12). Since comparison with results from similar studies in the United States suggests that most of the North American control population falls into the highest risk quintile of this score distribution, it would seem a hypothesis worth further study that these dietary variables can account for a major part of the international variation in large-bowel cancer incidence. Further studies are under consideration in Singapore and Mallorca.

Table 12. Distribution of cases and controls by a 'risk score' calculated on the basis of consumption of discriminatory food items

| Risk score | Cases | Controls | Relative risk | 95 % Confidence interval |
|---|---|---|---|---|
| 1 | 18 | 27 | 1.0 | |
| 2 | 11 | 28 | 0.6 | 0.2–1.6 |
| 3 | 14 | 27 | 0.8 | 0.3–2.1 |
| 4 | 25 | 12 | 3.1 | 1.1–8.7 |
| 5 | 32 | 6 | 8.0 | 2.5–26.7 |
| Total | 100 | 100 | | |

(*e*) *Study of diet in cancer epidemiology* (Dr J. Wahrendorf and Dr A. Geser; in collaboration with Dr O. M. Jensen, Danish Cancer Registry, Copenhagen; DEB/81/012)

A major methodological problem in research on nutrition and cancer concerns the instrument with which information on dietary habits is collected. The accuracy of questionnaire-derived historical dietary information, often used in epidemiological case-control studies, is difficult to study, and specific conditions are required. An interesting situation was met in Denmark where the Jutland Agricultural Association had carried out 28-day household investigations among volunteering members, starting as early as 1927. Household members who participated in these surveys in the two periods 1954–1957 and 1964–1966 were traced and asked to participate in a dietary interview, by which quantitative information on present and past dietary habits (at the time of the original survey), together with some information on demographic aspects and general changes in food habits was derived. The interview-derived information was compared with that from the original survey. The comparison was made for several food and nutritional items separately by first classifying the individuals into four equally large categories ('fourths') in respect of their consumption as reported in each of the three different sources of information. With this categorization, 4×4 tables were constructed to contrast the individuals' classification in two different sources of information. Table 13 contrasts in this way total energy and the three macrounutrients in the original survey and in the new interview on past food habits addressing the time of that survey.

If there were complete agreement between the two sources, all individuals should appear on the main diagonal of such a table. This is certainly not the case in the examples given, nor was it for other food or nutritional items. However, a certain clustering around the diagonal can be noted. The information in these tables was further condensed into rank correlation coefficients. Inspection of these led to the conclusions that:

(1) the highest correlations of the classifications were observed between interviews about present and interviews about past food consumption;

Table 13. Classification of study population in 'fourths' of their consumption of major nutrients as reported in original survey and in interview about past food consumption

| Diet item | Original survey | New interview | | | | Rank correlation |
|---|---|---|---|---|---|---|
| | | First[a] | Second | Third | Fourth | |
| Total energy | First | 10 | 6 | 4 | 0 | 0.417 |
| | Second | 4 | 7 | 6 | 3 | |
| | Third | 3 | 3 | 6 | 8 | |
| | Fourth | 3 | 4 | 4 | 8 | |
| Fat | First | 8 | 9 | 3 | 0 | 0.405 |
| | Second | 4 | 4 | 9 | 3 | |
| | Third | 5 | 5 | 4 | 6 | |
| | Fourth | 3 | 2 | 4 | 10 | |
| Carbohydrates | First | 9 | 6 | 4 | 1 | 0.335 |
| | Second | 4 | 5 | 8 | 1 | |
| | Third | 4 | 4 | 6 | 6 | |
| | Fourth | 3 | 5 | 2 | 9 | |
| Protein | First | 9 | 6 | 4 | 1 | 0.314 |
| | Second | 4 | 6 | 6 | 4 | |
| | Third | 2 | 5 | 8 | 5 | |
| | Fourth | 5 | 3 | 2 | 9 | |

[a] Refers to lowest 25 % of the distribution

(2) a good correlation of the classification from the original survey and the interview about past food was observed for total energy, fat, milk and fish consumption;

(3) the information derived for males shows closer correlations in all respects than that for females, the same being true for those individuals who, in general terms, reported that they had not changed their food habits over the years compared with those who said they had changed;

(4) supplementing information about present food consumption with information about particular changes of food habits led to the same degree of predictiveness as did detailed interviewing about past food habits.

The results of this study are reported in greater detail by Jensen *et al.*[42]

The consequences of such misclassification for case-control studies on diet and cancer can be highlighted by a constructed example. In Table 14 we considered a 'true' classification of cases and controls into four exposure categories with a clear gradient in relative risks. If the 'observed' data resulted from these by a misclassification of the order of magnitude seen so far, total energy in the study described above (Table 13), they would produce a much less pronounced gradient in relative risk. Thus, the effect of misclassification and, in addition, of the heterogeneity of study populations, might show moderate effects in case-control studies on diet and cancer but in fact represent substantial, true risk gradients.

[42] Jensen, O. M., Wahrendorf, J., Rosenquist, A. & Geser, A (1983) (submitted for publication).

Table 14. Artificial data from a case-control study with misclassification

| | | Category 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| 'True' data | cases | 10 | 40 | 60 | 100 |
| | controls | 100 | 100 | 100 | 100 |
| | relative risk | 1.0 | 4.0 | 6.0 | 10.0 |
| 'Observed' data | cases | 38 | 47 | 53 | 72 |
| | controls | 101 | 101 | 101 | 97 |
| | relative risk | 1.0 | 1.24 | 1.39 | 1.97 |

*(f) Studies on alcohol and cancer*

This programme was started initially to investigate the role of alcohol in oesophageal cancer in Brittany and Normandy. In the course of time, however, it has progressively been extended to other cancer sites in various countries and to the simultaneous study of other risk factors such as smoking and diet, since, from the first stages, the combination of the various factors appeared to be of major importance.

(i) *Oesophageal and other cancers in Normandy* (Dr A. J. Tuyns, Dr J. Estève and Mrs A. Arslan; in collaboration with Dr A. Péquignot, Nutrition Section, INSERM, Le Vésinet, France)

The drinking pattern of the population sample used as a control group for the various studies in Calvados has been further analysed. It is clearly changing from one generation to another: on the one hand, younger people tend to drink less cider and digestives than their parents but they consume more beer[43]; on the other hand, the lower average daily intake of alcohol among older men as compared with middle-aged adults can be understood after analysing available information on previous alcohol consumption. After age 45, men tend to drink progressively less. A comparison of present consumption and life-time consumption also showed that changes occur in amounts consumed but not in kind of beverage. These analyses are of interest for defining the behaviour of individuals towards alcoholic beverages; they also show that, to study the risk of disease related to ethanol, a parameter of consumption must be used that takes into account previous consumption, for example, life-time average daily intake[44]. A similar exercise in relation to smoking led to similar conclusions concerning tobacco consumption[45].

Liver cirrhosis is one of the most commonly observed consequences of drinking. The straightforward dose-response effect relating risk of ascitic cirrhosis to average daily intake of alcohol, which was described previously in a first case-control study in Ille-et-Vilaine, has now been confirmed by a similar analysis in Calvados. In addition, it has been observed that the risk increases much more quickly in women than in men; in other words, for a similar level of daily consumption, the risk of developing cirrhosis is much higher in women than in men. This confirms an observation made by clinicians[46]. Since this effect may be related to the particular sensitivity of

[43] Tuyns, A. J., Péquignot, G. & Hu, M. X. (1983) *Rev. Epidemiol. Santé publ.* (in press).
[44] Tuyns, A. J. & Estève, J. (1983) *Rev. Epidemiol. Santé publ.* (submitted for publication).
[45] Tuyns, A. J. & Hu, M. X. (1982) *Br. J. Addict.*, 77, 167–183.
[46] Tuyns, A. J., Péquignot, G. & Estève, J. (1983) *Int. J. Epidemiol.* (in press).

the female liver, it may also be applicable to the cancer sites known to be linked with alcohol consumption. In a preliminary study of the role of alcohol and tobacco on various segments of the digestive tract, it was shown that none of the gastrointestinal cancers was related significantly either to alcohol or to tobacco, with the exception, of course, of oesophageal cancer[47].

Further studies are now under way on this particular site. In a first attempt to look at a 'pure' risk related to either alcohol or tobacco, the risks of developing oesophageal cancer have been calculated for non-drinking smokers and for non-smoking drinkers[48]. Each factor was shown to have an effect independent of the other; this observation is consistent with the multiplicative model described previously in Ille-et-Vilaine but not with the concept that the role of ethanol can be reduced to that of enhancing the carcinogenic role of tobacco. The finding is further strengthened by the observation among the small group of women (39 out of a total of 743 cases) that none was a smoker but many were drinkers. Calculation of the risks related to alcohol showed levels very similar to those observed in men; thus, in contrast to our finding for cirrhosis, a given level of alcohol consumption carries the same risk for women as for men. As a consequence of this observation, the very high sex ratio (nearly 20:1) could be ascribed entirely to the sex gradient in drinking patterns, in the particular context of Calvados.

Salt has been suspected to be associated with gastric and perhaps other cancers of the digestive tract. Consumption of various types of salted food has been found to entail an increased risk of cancer of the stomach in several parts of the world. The material collected in Calvados provided an opportunity to examine the role of salt in cancer of the digestive tract: there was a significantly elevated risk for oesophageal cancer, and the risk was also higher for gastric and colon cancer and, rather surprisingly, for ascitic cirrhosis[49]. This pointed to a possible side effect associated with alcohol consumption. After adjusting for alcohol consumption, however, the role of salt disappeared completely for oesophageal cancer and for cirrhosis and was reduced for gastric cancer[50]. This finding indicates how prudent one must be in considering factors entailing moderately increased relative risks which may be due to an association with another—more significant—risk factor.

Ascorbic acid (vitamin C) is believed to have a protective role against cancers at several sites in the digestive tract, as it might impede the formation of *N*-nitrosamines (see p. 54). In Calvados, citrus fruit and juices are the most important source of vitamin C, and it was possible to calculate the risk of oesophageal cancer among consumers of these foods *versus* non-consumers: a reduction of about 50% was observed. When this effect was looked at separately for two levels of alcohol consumption, the same results were obtained; it is thus independent of the role of alcohol[51]. This finding confirms similar observations made in other regions.

(ii) *Laryngeal and hypopharyngeal cancer in southern Europe* (Dr A. J. Tuyns, Dr J. Estève and Mrs A. Arslan; in collaboration with Dr A. Zubiri, Cancer Registry of Zaragoza, Spain; Dr A. del Moral, Health Department of Navara, Pamplona, Spain; Dr B. Terracini, Institute of Pathology, University of Turin, Italy; Dr F. Berrino, National Cancer Institute, Milan, Italy; Mr L. Raymond, Geneva Cancer Registry, Switzerland; and Dr H. Sancho-Garnier and Dr E. Benhamou, Gustave Roussy Institute, Villejuif, France)

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[47] Tuyns, A. J., Péquignot, G., Gignoux, M. & Valla, A. (1982) *Int. J. Cancer*, **30**, 9–11.
[48] Tuyns, A. J. (1983) *Int. J. Cancer* (submitted for publication).
[49] Tuyns, A. J. (1983) *Nutr. Cancer*, **4**, 198–205.
[50] Tuyns, A. J. (1983) *Nutr. Cancer* (in press).
[51] Tuyns, A. J. (1983) *Nutr. Cancer* (submitted for publication).

Laryngeal and hypopharyngeal cancers are particularly prevalent in the southern countries of Europe, and a study has been designed with the collaboration of the centres listed above. The roles of tobacco, alcohol and occupation will be studied. Field collection of information on cases and controls is practically terminated at most centres, and this information has been entered in a computer and validity checks started. These first analyses will be conducted in the second half of 1983.

Dr W. Lehman, Geneva, who is acting as referee for the clinical part of the study, is also in charge of coding the clinical questionnaire. This part of the work, which has now been terminated for the cases observed in Caen, Calvados, was needed to ascertain the exact starting point of the cancer, as the environmental factors acting on the various subsites may vary in intensity, as suggested by preliminary analysis.

(iii) *Review articles on alcohol and cancer* (Dr A. J. Tuyns)

The role played by alcohol in human cancer has attracted considerable attention in the scientific community. The subject has been reviewed on several occasions at meetings and in publications[52-55].

## 5. GENETICS AND CANCER

(*a*) *Identification of genetic predisposing conditions* (Dr G. Lenoir)

A new project is being implemented to evaluate whether genetic predisposing conditions can be identified in cancers arising within the general population. The proposed approach is to do linkage studies in multiple-case families by analysing the genetic make-up of individuals, using highly polymorphic DNA markers. The first step is to establish a collection of lymphoblastoid cell lines—as a source of constitutional DNA—from members of families within which multiple cases of cancer have arisen. This is being implemented for breast cancer, nasopharyngeal carcinoma and retinoblastoma.

(*b*) *Association between HLA profile and nasopharyngeal carcinoma* (Professor S. H. Chan)

During the year, Professor Chan (Department of Microbiology, University of Singapore) has been a visitor to the Biostatistics Unit. A paper summarizing the association between carcinoma of the nasopharynx and the HLA system, loci A and B, has been accepted for publication[56]. The results of tissue typing since the identification of the antigen SIN-2 (now BW46) in 1973 are given, as shown in Table 15.

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[52] Tuyns, A. J. (1982) In: Schottenfeld, D. & Fraumeni, J. F., eds, *Cancer Epidemiology and Prevention*, Philadelphia, Saunders, pp. 293–303.
[53] Tuyns, A. J. (1982) In: Pfeiffer, C. J., ed., *Cancer of the Esophagus*, Vol. 3, Boca Raton, FL, CRC Press, pp. 3–18.
[54] Tuyns, A. J. (1983) In: Schlierf, G., ed., *Ernährung und Krebs*, Stuttgart, Wissenschaftliche Verlagsgesellschaft.
[55] Tuyns, A. J. (1983) In: Morgan, M. Y., ed., *Alcohol and Disease*, London, Churchill Livingston (in preparation).
[56] Chan, S. H., Day, N. E., Kunaratnam, N., Chia, K. B. & Simons, M. J. (1983) *Int. J. Cancer*, **32**, 171–176.

Table 15. HLA antigen frequencies of newly diagnosed Singapore Chinese patients with nasopharyngeal cancer (NPC) and controls in three separate studies

| HLA locus | | STUDY 1 NPC n = 141 | STUDY 1 Control n = 238 | STUDY 2 NPC n = 172 | STUDY 2 Control n = 92 | STUDY 3 NPC n = 63 | STUDY 3 Control n = 38 | TOTAL NPC n = 366 | TOTAL Control n = 368 |
|---|---|---|---|---|---|---|---|---|---|
| A | 1 | 0.7 | 0 | 3.5 | 0 | 0 | 2.6 | 1.9 | 0.3 |
| | 2 | 61.0 | 52.9 | 64.5 | 57.6 | 64.2 | 44.7 | 63.1 | 53.3[a] |
| | 3 | 0.7 | 0.4 | 1.7 | 1.1 | 1.9 | 2.6 | 1.4 | 0.8 |
| | 9 | 33.3 | 27.3 | 29.1 | 28.3 | 35.8 | 26.3 | 31.7 | 27.4 |
| | 10 | 9.2 | 5.0 | 3.5 | 9.8 | 7.5 | 13.2 | 6.3 | 7.1 |
| | 11 | 40.4 | 60.5 | 44.2 | 53.3 | 37.7 | 60.5 | 41.8 | 58.7[b] |
| | 28 | 0 | 0.4 | 0 | 0 | 1.9 | 2.6 | 0.3 | 0.5 |
| | 29 | 0.7 | 1.3 | 0.6 | 0 | 0 | 0 | 0.5 | 0.8 |
| AW | 19 | 15.6 | 20.6 | 26.7 | 21.7 | 24.5 | 23.8 | 22.1 | 20.4 |
| B | 5 | 13.5 | 12.6 | 11.6 | 8.7 | 13.2 | 18.4 | 12.6 | 12.2 |
| | 7 | 0.7 | 1.7 | 0.6 | 1.1 | 0 | 0 | 0.5 | 1.4 |
| | 8 | 0.7 | 0.4 | 0 | 0 | 0 | 5.3 | 0.3 | 0.8 |
| | 12 | 1.4 | 3.4 | 2.3 | 3.3 | 3.8 | 0 | 2.2 | 3.0 |
| | 13 | 13.5 | 20.2 | 7.6 | 16.3 | 7.5 | 15.8 | 9.8 | 13.8[c] |
| | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 15 | 18.4 | 22.3 | 25.6 | 19.6 | 24.5 | 28.9 | 22.7 | 22.3 |
| | 17 | 28.4 | 14.3 | 25.6 | 13.0 | 24.5 | 18.4 | 26.5 | 14.4[d] |
| | 18 | 0.7 | 1.7 | 1.7 | 0 | 3.8 | 0 | 1.6 | 1.1 |
| | 27 | 2.8 | 7.1 | 2.3 | 6.5 | 3.8 | 0 | 2.7 | 6.3 |
| | 37 | 1.4 | 0.4 | 0 | 0 | 0 | 0 | 0.5 | 0.3 |
| | 40 | 37.6 | 41.2 | 43.6 | 46.7 | 30.2 | 44.7 | 39.3 | 42.9 |
| BW | 16 | 9.9 | 10.9 | 13.4 | 14.1 | 9.4 | 23.7 | 11.5 | 13.0 |
| | 21 | | | 0 | 0 | 0 | 0 | 0 | 0 |
| | 22 | 6.4 | 12.2 | 7.6 | 12.0 | 9.4 | 15.8 | 7.4 | 12.5 |
| | 35 | 5.7 | 5.0 | 3.5 | 7.6 | 13.2 | 2.6 | 5.7 | 5.4 |
| | 46 | 34.0 | 22.7 | 37.2 | 27.2 | 37.7 | 15.8 | 36.1 | 23.1[e] |

Differences between total NPC and control:

| | $\chi$ | p | $p_c$ | RR |
|---|---|---|---|---|
| *a* | 6.92 | <0.01 | NS | 1.5 |
| *b* | 20.28 | $3\times10^{-6}$ | $8\times10^{-5}$ | 0.5 |
| *c* | 11.18 | <0.001 | <0.02 | 0.47 |
| *d* | 15.79 | $6.8\times10^{-4}$ | 0.002 | 2.14 |
| *e* | 14.20 | $1.7\times10^{-4}$ | 0.004 | 1.88 |

## 6. ROLE OF VIRUSES IN THE ETIOLOGY OF HUMAN CANCER (Dr G. Lenoir, Miss C. Bonnardel, Mrs M. F. Lavoué and Mrs S. Pauly; Dr A. Geser, Dr D. M. Parkin and Dr N. E. Day; in collaboration with Dr G. Brubaker, Shirati Mission Hospital, Tanzania, DEB/71/007; and Dr C. C. Draper, Ross Institute, London School of Hygiene and Tropical Medicine, DEB/82/018)

The main objectives of this programme are to evaluate, using laboratory investigations linked to epidemiological studies, the role of viruses and of chromosomal rearrangements in the etiology of human cancer. Most of the studies have involved Burkitt-type lymphoma (BL), a cancer known to show great geographic variation in its incidence and to be associated with a virus, the Epstein-Barr virus (EBV). Whereas past studies had a mainly sero-epidemiological orientation, during the past four years, BL tumours collected from different geographic areas have been studied from

cytological, virological, immunological, cytogenetic and biochemical points of view. This approach led recently to the discovery that, in BL cases, whereas the association with EBV is not a constant characteristic, specific chromosomal rearrangements are always detected in the tumour cells (see p. 92). These may represent a crucial step in the development of the malignant process through the transposition and activation of cellular oncogenes.

(*a*) *Studies on Burkitt's lymphoma in central Africa*

Most of the studies of the role of EBV in high-incidence areas of Africa are now terminated, and the results are being analysed and published.

A final case report from the Ugandan prospective study conducted in the West Nile district[57] indicated that elevated anti-viral capsid antigen EBV antibody titres occur up to six years before development of tumours, confirming the hypothesis that BL may be initiated very early in life and bringing additional epidemiological evidence for the role of the virus in BL.

Detection of EBV markers by molecular means indicated that in East Africa a small proportion (4%) of BL occurring in high-incidence areas, such as central Africa, are not associated with the virus and are therefore closely comparable to BL-type lymphoma arising in low-incidence areas such as Europe and North America[58].

In order to determine whether the decline in BL incidence observed in Tanzania can be related to changes in the pattern of EBV infection, a serological survey, done in collaboration with Dr G. Brubaker (Shirati Mission Hospital, Musoma, Tanzania), has been performed on two sequential series of 300 children. Statistical analysis of the results is in progress.

(*b*) *Studies on Burkitt-type lymphoma in north Africa* (in collaboration with Dr M. Aboulola, CHU Mustapha, Alger, Algeria, DEC/82/015; and Dr T. Philip, Centre Léon-Bérard, Lyon, France)

Algeria has always been considered a low-incidence area for BL. Our study, based on an analysis of about 50 cases, indicated that the clinical presentation of the disease in Algeria is comparable with that observed in the USA and Europe. However, when the EBV-BL association is evaluated by detecting viral markers within the malignant cells, the great majority of Algerian BL cases (over 95%) are found to be EBV-associated, as in high-incidence areas of central Africa. This suggests that the association may be related to socio-economic status and thus to age at primary infection.

(*c*) *Studies on Burkitt-type lymphomas in France* (in collaboration with Dr T. Philip, Centre Léon-Bérard, Lyon, France)

The studies conducted in the past permitted a better clinical and pathological characterization of the disease in a low-incidence area[59]. Virological investigations have now shown that less than 20% of the tumours are EBV-associated, and that some of the rare EBV-associated lymphomas might follow infectious mononucleosis or Hodgkin's disease.

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[57] Geser, A., de Thé, G., Lenoir, G., Day, N. E. & Williams, E. H. (1982) *Int. J. Cancer*, **29**, 397–400.

[58] Geser, A., Lenoir, G. M., Andersson-Anvret, M., Bornkamm, G., Klein, G., Williams, E. H., Wright, D. H. & de Thé, G. (1983) *Eur. J. Cancer clin. Oncol.* (in press).

[59] Philip, T., Lenoir, G. M., Bryon, P. A., Gerard-Marchant, R., Souillet, G., Philippe, N., Freycon, F. & Brunat-Mentigny, M. (1982) *Br. J. Cancer*, **45**, 670–678.

## 7. BIOCHEMICAL, METABOLIC AND CYTOGENETIC PARAMETERS AS INDICATORS OF INDIVIDUAL SUSCEPTIBILITY TO CHEMICALLY-INDUCED CANCER

(a) *Biochemical and cytogenetic parameters as indicators of individual susceptibility to* N-*nitroso compound-induced cancer in rodents* (Dr A. Aitio, Dr M.-L. Aitio, Miss A. M. Camus, Dr M. Friesen, Dr J. R. P. Cabral, Miss R. Cartier, Mrs L. Garren, Mrs E. Robert and Mrs D. Galendo; in collaboration with Dr H. Norppa, Dr M. Sorsa, Dr K. Hemminki and Ms H. Lax, Institute of Occupational Health, Helsinki; DEC/81/032)

Metabolic parameters that may determine differences in individual susceptibility to chemically-induced cancer are being investigated in rats. In parallel, early markers of genetic damage are being examined to establish whether they can serve as indicators of individual cancer risk. The activities of drug and carcinogen metabolizing enzymes were determined *in vitro* using liver samples obtained by partial hepatectomy prior to carcinogen administration. The following enzyme activities were measured (the substrates are given in parentheses): monooxygenases (ethoxycoumarin, benzo[*a*]pyrene, *N*-nitrosodimethylamine), epoxide hydrolase (benzo[*a*]pyrene-4,5-oxide), glutathione S-transferase (benzo[*a*]pyrene-4,5-oxide) and UDP-glucuronosyl transferase (4-methylumbelliferone).

The enzymatic capacity of rat liver fractions to remove $O^6$-ethylguanine from ethylated DNA template *in vitro* was also measured. Individual metabolic capacities were determined *in vivo* by monitoring the metabolites of two predictor drugs, antipyrine and disopyramide, in the urine before starting administration of the carcinogen and twice during dosage.

The outbred rats were then dosed with *N*-nitrosodiethylamine (NDEA), a hepatocarcinogen which requires metabolic activation by liver monooxygenases. During the administration of NDEA, attempts were made to monitor covalent binding products excreted in the urine. In preliminary experiments, radiolabelled NDEA and *N*-nitrosodimethylamine (NDMA) were administered to rats: four-day urines contained 15% and 2.4% of the dose of NDEA and NDMA, respectively; however, only 0.003% of the urinary radioactivity was identified as 7-ethylguanine, while the corresponding proportion for 7-methylguanine was 1%. Thus, excretion of 7-ethylguanine into urine was so low that results in individual rats could not be reliably determined. When 7-ethylguanine was injected into rats, it was excreted almost quantitatively into urine. Furthermore, the administration of NDEA did not result in a large excretion of alkylated cysteine residues, in contrast to results obtained with NDMA. When purified ethylcysteine was injected into rats, it was excreted almost quantitatively into urine as *N*-acetylethylcysteine. The results indicate large differences in the metabolic fate of carbons derived from NDEA and NDMA: while the urinary excretion products of NDEA appeared to be mostly common metabolites, the NDMA reaction products included identifiable methylated DNA base adducts[60].

During carcinogen administration, some reaction products of the carcinogen with DNA and proteins, i.e., alkylation of haemoglobin and urinary excretion of thioethers, were monitored. Individual susceptibility to the carcinogen (absence or presence of tumours and length of latency) will be correlated with the biochemical markers measured. The validity of cytogenetic parameters in predicting tumour susceptibility is being studied by correlating sister chromatid exchange rates in lymphocytes with the presence or absence of tumours and with latency in rats given *N*-ethyl-*N*-nitrosourea.

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[60] Hemminki, K. (1983) *Arch. Toxicol.*, **52**, 249–285.

In separate experiments, the urines of treated and control rats are being analysed for the content of modified ribonucleosides, to test the hypothesis that an elevated ribonucleoside excretion is an early signal of tumour development[61].

(*b*) *Studies on benzo[a]pyrene metabolism in surgical lung tissue and mucosa specimens from lung cancer and cancer-free patients* (Dr E. Hietanen, Dr A. Aitio, Miss A. M. Camus and Dr R. Saracci; in collaboration with Professor C. Giuntini, National Research Council, University of Pisa, Italy; and Dr H. V. Gelboin, National Cancer Institute, Bethesda, MD, USA)

Enzyme activities related to the metabolic activation of carcinogens (benzo[*a*]pyrene hydroxylation and ethoxycoumarin *O*-deethylation) and to the inactivation of reactive intermediates (epoxide hydration, glutathione S-conjugation, glucuronide conjugation and glutathione contents) are being determined in lung tissue specimens from patients with lung cancer and other pulmonary diseases. The role of individual cytochrome P-450 isozyme species will be tested utilizing monoclonal antibodies.

The data will be related to information on the living habits of patients, occupation, pulmonary function tests and diseases of the lungs. The study is in progress.

(*c*) *Purification of cytochrome P-450 catalysing demethylation of* N-*nitrosodimethylamine and preparation of its antibody* (Dr E. Hietanen and Miss A.-M. Camus; in collaboration with Dr M. Lang, Department of Pharmacology and Toxicology, University of Kuopio, Finland; DEC/83/004)

The cytochrome P-450-catalysed *N*-demethylation reaction is an essential step in the activation of many *N*-nitroso compounds to their ultimate carcinogens. Research related to this reaction has been hampered by the insensitivity of the methodology presently available. *N*-Nitroso compounds exert their carcinogenicity in many extrahepatic tissues of experimental animals and possibly man (oesophagus, stomach, colon, pancreas and brain); in some of these tissues, the presence of this *N*-demethylase activity has not been demonstrated.

The aims of the study are to develop sensitive methods for measuring enzyme activities responsible for the metabolism of nitroso compounds. First, *N*-nitrosodimethylamine *N*-demethylase activity will be characterized, and then the cytochrome P-450 species responsible for this reaction will be purified and characterized. Second, an antibody towards this cytochrome P-450 isozyme will be produced and immunoassays developed. These assays will be based on enzyme-linked immunosorbent P-450 and detection of this enzyme in tissues.

(*d*) *Hepatic drug metabolism and liver microsome-mediated mutagenicity of carcinogens in rat strains characterized as slow and fast metabolizers of debrisoquine* (Dr E. Hietanen, Mr C. Malaveille, Miss A. M. Camus, Mr J. C. Bérézíat and Mrs G. Brun; in collaboration with Dr J. C. Idle and Dr J. C. Ritchie, St Mary's Hospital Medical School, London)

Hydroxylation of debrisoquine *in vivo* has been proposed as a probe to assess individual drug handling capacity and to classify those individuals into slow and fast metabolizers[62]. In order to

[61] Thomale, J. & Nass, G. (1982) *Cancer Lett.*, **15**, 149.

[62] Ritchie, J. C. & Idle, J. R. (1982) In: Bartsch, H. & Armstrong, B., eds, *Host Factors in Human Carcinogenesis (IARC Scientific Publications No. 39)*, Lyon, International Agency for Research on Cancer, pp. 391–394.

study this genetic polymorphism in animals, DA and Lewis rat strains (slow and fast metabolizers) were used; these strains showed remarkably different toxicological responses to aflatoxin $B_1$, the Lewis rats being more sensitive[63].

We therefore studied hepatic microsomal enzyme activities and hepatic 9000 × *g* supernatant-mediated mutagenesis in female DA and Lewis rats. The differences found in cytochrome P-450 contents and monooxygenase activities, however, were only 30–40%, except for the total testosterone metabolism, which was 50% lower in the livers of DA rats than in Lewis rats. Mutagenicity studies using *N*-nitrosomorpholine, 2-acetylaminofluorene, benzo[*a*]pyrene 7,8-diol and aflatoxin $B_1$ as promutagens revealed four times higher mutagenic activation of aflatoxin $B_1$ when using a supernatant fraction from Lewis rats than from DA strain rats. The data thus suggest the existence of a specific, minor cytochrome P-450 isozyme responsible for the 4-hydroxylation of debrisoquine[64]. Further induction studies to characterize this cytochrome are in progress.

(*e*) *Effect of dietary constituents on lipid peroxidation/foreign compound metabolism and its role in tumour initiation/progression* (Dr E. Hietanen, Dr V. Koblyakov, Mr J. C. Béréziat and Miss A. M. Camus; in collaboration with Dr T. Heinonen, Institute of Occupational Health, Helsinki; and Dr H. V. Gelboin, National Institutes of Health, Bethesda, MD, USA)

A significant role in the development of cancers in man has been attributed to dietary components[65, 66]. The action of xenobiotics entering the body as food contaminants, the modulation of cancer formation by nutrients, and natural products themselves must be considered[67]; whether nutrients act as tumour 'promoters' or whether they modulate the initiation process is still unresolved. Many epidemiological studies in which dietary fat and cholesterol intake are compared with cancer incidences or mortality have shown a relation between dietary lipids and the risk of breast, colon and lung cancers[68, 69]; however, some studies have shown an inverse relationship between total cancer deaths (from colon cancer especially) and serum cholesterol concentration[70, 71], despite the fact that dietary lipid (cholesterol) intake usually elevates serum cholesterol.

Although experimental studies have established a link between dietary lipids, especially polyunsaturated ones, and chemically induced cancer[72–73], little is known about the underlying mechanisms. Several hypotheses have been proposed: (1) dietary constituents may modulate hormonal levels and tissue responses to hormones when hormone-sensitive cancers are concerned[74]; (2) dietary constituents, e.g., lipids, proteins or vitamins, may alter the activities of enzymes producing reactive intermediates from xenobiotics or might modulate free radical reac-

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[74] Welsch, C. W. & Aylsworth, C. F. (1983) *J. natl Cancer Inst.*, **70**, 215–221.

tions[75, 76]. Whatever the mechanism of action may be, DNA damage and possible tumour formation may result[77, 78]. Dietary constituents have been shown previously to play an important role in the regulation of hepatic and extrahepatic drug metabolism both in man[79–80] and in experimental animals, although the significance of these changes for tumour induction has not been evaluated.

We therefore initiated two series of experiments: (1) in-vitro experiments in which the effects of selected carcinogens and other xenobiotics on the formation of free radicals (measured as activated oxygen-initiated chemiluminescence and lipid peroxidation in primary rat hepatocytes) are studied and the role of individual cytochrome P-450 isozymes in the free-radical formation of carcinogens is evaluated (by the consumption of free radicals by trapping agents such as glutathione); (2) short-term induction studies of the role of various cytochrome P-450 isozymes in the metabolic activation of carcinogens in mouse liver (by inhibiting individual P-450 isozymes by respective monoclonal antibodies). Both 'responsive' and 'non-responsive' mice are being used. Short-term feeding studies in rats are under way to elucidate the role of dietary lipids (fats and cholesterol) in the modulation of cytochrome P-450 catalysing the hydroxylation of endogenous substrates. The dietary modulation of free-radical formation from xenobiotics will thus be evaluated, using hepatocytes from these treated animals as a biological model and measuring the effects of free radicals as a change in chemiluminescence and induced lipid peroxidation.

In long-term feeding studies, a group of rats will receive either a high-fat or low-fat diet or a high-cholesterol or cholesterol-free diet. Prior to feeding, an initiating dose of carcinogens will be given. During the course of the study, blood glutathione level, glutathione peroxidase and superoxide dismutase activities will be measured. Animals will also be analysed for drug metabolizing enzyme activities in the liver and in extrahepatic tissues and for free-radical formation (lipid peroxidation, chemiluminescence) in hepatocytes. These biochemical parameters will be related to the absence or presence of cancer in each dietary group.

The aims of these studies are: (1) to investigate the role of dietary lipids in experimental carcinogenesis; (2) to study the sequence of changes in biochemical 'markers' in tumour formation; and (3) to select possible blood or urine markers that reflect relevant biochemical changes involved in tumour induction/progression. Such markers, should they be found, can be explored in human studies.

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# STUDIES ON MECHANISMS OF CARCINOGENESIS

## 1. STUDIES ON DNA REPAIR AND METABOLISM OF CARCINOGENS

During the last year, particular emphasis was placed on examining the capacity of tissues and cells originating from humans, monkeys and various other mammalian species to repair DNA adducts produced by alkylating agents. The studies are aimed at assessing the role of DNA repair processes in determining, qualitatively and quantitatively, the susceptibilities of different species or tissues to carcinogenic agents.

(*a*) *Modulation of DNA repair in parenchymal and non-parenchymal rat liver cells* (Dr A. Likhachev, Dr R. Montesano, Mrs G. Planche-Martel and Miss O. Deblock)

Previous studies[1] have shown that chronic administration of *N*-nitrosodimethylamine (NDMA) to rats is followed by an increase in the repair of $O^6$-methylguanine in liver DNA. The present study has been extended to examine this increased repair capacity in both parenchymal and non-parenchymal liver cells. Preliminary results indicate that it is confined to the parenchymal cells and does not occur in endothelial or Kuppfer cells. It is of interest to note that the great majority of liver tumours induced by NDMA in BD rats are haemangioendothelial sarcomas and not hepatocellular tumours.

(*b*) *Effects of age on DNA methylation and repair in rats exposed to* N-*methyl*-N-*nitrosourea* (Dr A. Likhachev and Miss O. Deblock; in collaboration with Dr V. Anisimov, Dr A. Ovsyannikov and Dr M. Korsakov, N. N. Petrov Research Institute of Oncology, Leningrad, USSR)

Earlier experiments showed that the formation of methylating species in young rats exposed to *N*-methyl-*N*-acetoxymethylnitrosamine proceeded faster than in similarly treated old rats, and that the pattern of DNA methylation and repair in various tissues was different in the animals of these two age groups[2].

Experiments are under way to study the effect of ageing on the persistence of DNA methylated purines in various rat tissues exposed to *N*-methyl-*N*-nitrosourea.

(*c*) *Removal of* $O^6$-*methylguanine from DNA by mammalian tissue extracts* (Dr J. Hall, Miss H. Brésil and Dr R. Montesano; in collaboration with Dr C. von Bahr, Karolinska Institute, Laboratory of Clinical Pharmacology, Huddinge, Sweden; DEC/81/025)

[1] Montesano, R., Brésil, H., Planche-Martel, G., Margison, G. P. & Pegg, A. E. (1983) *Cancer Res.* (in press).
[2] Likhachev, A. J., Ohshima, H., Anisimov, V. N., Ovsyannikov, A. I., Revskoy, S. Y., Keefer, L. K. & Reist, E. J. (1983) *Carcinogenesis* (in press).

It was demonstrated previously that human and rat liver have an enzymatic activity capable of repairing $O^6$-methylguanine by a mechanism similar to that found in bacteria[3,4]. These studies have been extended to other mammalian tissues, with particular reference to extrahepatic tissues and the repair of higher alkylated derivatives using an in-vitro assay system that quantitates the removal of the $O^6$-alkylguanine from a radioactively labelled DNA substrate. The sensitivity of the assay system has been increased by the removal of carrier DNA during the incubation period; this was found to be particularly important when substrates with low levels of modification were being used. Sensitivity has been further increased by the use of high-performance liquid chromatography techniques to separate the alkylated bases.

In monkeys, $O^6$-methylguanine repair activity was found in liver and in extrahepatic tissue extracts (lung, kidney and brain) with the highest level of activity in liver (Fig. 6); similar levels were found in monkey and human liver (Fig. 7).

The removal of $O^6$-methylguanine has been studied in nine AT lymphoblastoid cell lines: six had similar levels of removal activity, while three had no detectable activity. These differences are being investigated further.

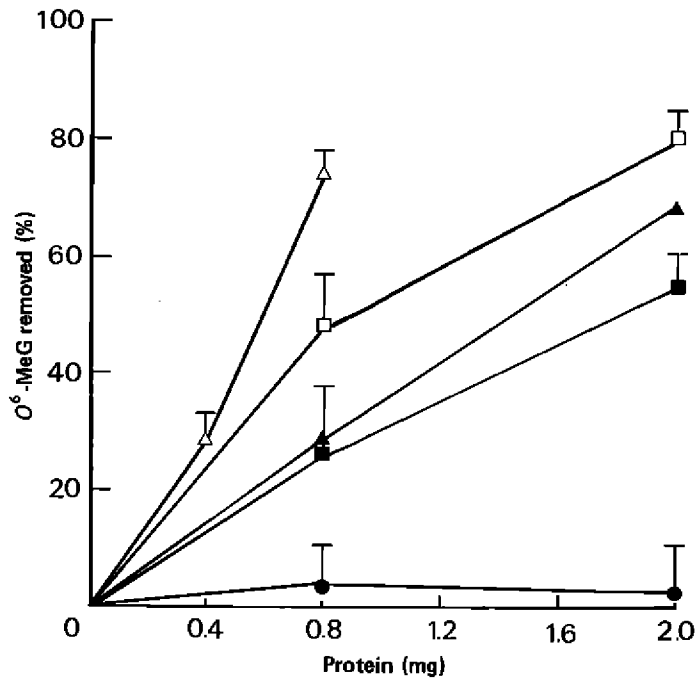



Fig. 6. Repair of $O^6$-methylguanine ($O^6$-MeG) by monkey extrahepatic tissue extracts. △, liver; □, lung; ▲, kidney; ■, brain; ●, colon mucosa. Alkylated DNA containing 0.32 pmol $O^6$-MeG; no carrier DNA present during incubation (60 min, 37°C).

[3] Pegg, A. E., Roberfroid, M., Von Bahr, C., Foote, R. S., Mitra, S., Brésil, H., Likhachev, A. & Montesano, R. (1982) *Proc. natl Acad. Sci. USA*, 79, 5162–5165.

[4] Montesano, R., Brésil, H. & Pegg, A. E. (1982) In: Magee, P. N., ed., *Nitrosamines and Human Cancer (Banbury Report 12)*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 141–152.

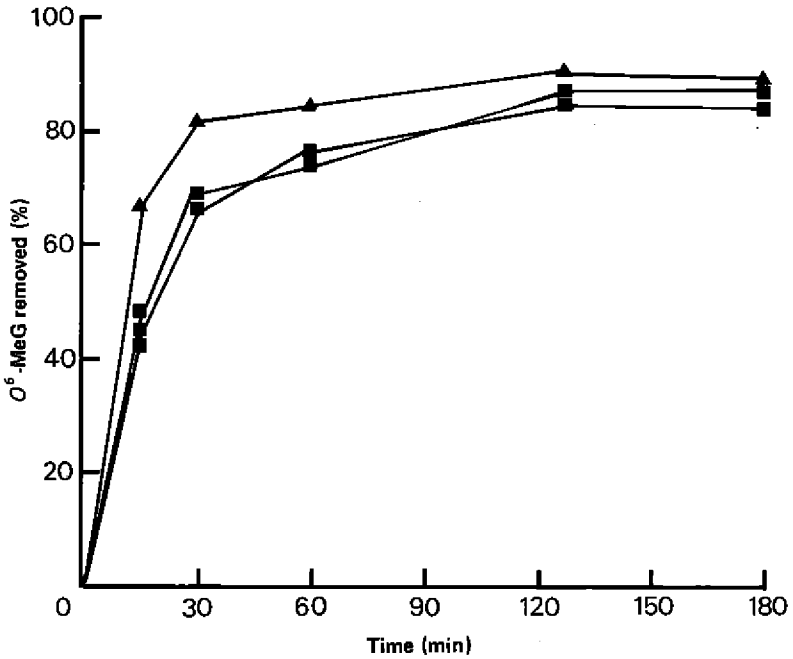



Fig. 7. $O^6$-Methylguanine ($O^6$-MeG) removal by human (▲) and monkey (■) liver extracts (2); 0.8 mg protein added. Alkylated DNA containing 0.32 pmol $O^6$-MeG; no carrier DNA present during incubation.

(*d*) *Activation of dibenzo*[a,e]*fluoranthene into bacterial mutagens* (Mr C. Malaveille and Mme A. Hautefeuille; in collaboration with Dr O. Perin-Roussel; Dr. S. Saguem, Dr M. Croisy-Delcey and Dr F. Zajdela, INSERM, Fondation Curie, Institut du Radium, Orsay, France)

Dibenzo[*a,e*]fluoranthene, a powerful carcinogen in mice, has been reported to occur in products of incomplete combustion. Since the *Salmonella*/microsome assay has been shown to be helpful in pinpointing reactive intermediates of polynuclear aromatic hydrocarbons, we have compared the rat and mouse liver 9000 × *g* supernatant-mediated mutagenicities of DBF and of its 7-monohydroxy, 3,4- and 12,13-diol derivatives in *S. typhimurium* TA100 strain; three synthetic, structurally related hydrocarbons were also tested. Of these compounds, the 12,13-dihydrodiol showed the highest activity, being 6-10 times more mutagenic than the parent compound. Our data, in conjunction with those of previous studies on the liver microsomal metabolism and DNA binding of dibenzo[*a,e*]fluoranthene and its dihydrodiols, indicate that its activation to bacterial mutagens may occur predominantly through a vicinal, non-bay-region 12,13-dihydrodiol-epoxide[5].

[5] Malaveille, C., Hautefeuille, A., Perin-Roussel, O., Saguem, S., Croisy-Delcey, M., Zajdela, F. & Bartsch, H. (1983) (submitted for publication).

(*e*) *Activation of dimethylnitramine into alkylating and mutagenic agents* (Mr C. Malaveille, Mrs G. Brun and Dr A. Likhachev; in collaboration with Dr A. Croisy, INSERM, Fondation Curie, Institut du Radium, Orsay, France, DEC/80/018; and Dr H. Rosenkranz, Case Western Reserve, University of Cleveland, OH, USA)

*N*-Nitramines can be produced as atmospheric pollutants when dinitrogen tetraoxide reacts with secondary amines. Dimethylnitramine (DMNO) and diethylnitramine have been shown to produce liver and kidney tumours in rodents; and DMNO and some other nitramines are metabolized into bacterial mutagens in the presence of rat liver post-mitochondrial supernatant[6] (S9). As a follow-up, we have investigated the metabolic activation pathways of DMNO in more detail[7]: DMNO undergoes hydroxylation in the presence of rat liver S9 to yield hydroxymethyl-methylnitramine (OH-MNO), which displayed a 100-fold higher mutagenic activity in *Salmonella typhimurium* TA100 strain than DMNO. The mutagenicity of DMNO in the presence of S9 paralleled the formation of OH-MNO. OH-MNO showed no alkylating activity towards nicotinamide, implicating it as a proximate mutagenic metabolite of DMNO. DMNO was found to be more mutagenic in a nitroreductase(s)-proficient (TA100) than in a deficient (TA100NR) strain; after reduction of OH-MNO with zinc-ammonium chloride, it yielded an agent(s) which alkylated nicotinamide implying a reduction of the nitro group in OH-MNO to yield a hydroxylamino derivative as the ultimate (or penultimate) mutagenic metabolite. Work is in progress to elucidate the DNA binding adducts produced by DMNO following its metabolic activation and to characterize the nitroreductase(s) involved.

## 2. BIOLOGICAL CONSEQUENCES OF CARCINOGEN-DNA ADDUCTS AND THEIR DETECTION BY ANTIBODIES

(*a*) *Studies on vinyl chloride* (Mr A. Barbin and Mr J. C. Béréziat; in collaboration with Dr R. J. Laib, Institute of Pharmacology, Toxicology Unit, University of Mainz, FRG; Professor M. F. Rajewsky, Institute for Cell Biology, University of Essen, FRG, DEC/81/003; Professor G. Michel, Université Claude-Bernard, Lyon, France; Dr M. Radman, Department of Molecular Biology, Free University of Brussels, Rhode St Genese, Belgium)

The mutagenic and carcinogenic effects of vinyl chloride are thought to result from the reaction of metabolites, especially chloroethylene oxide, with DNA. Up to the present, three vinyl chloride-DNA adducts have been identified *in vitro* and *in vivo:* 1,$N^6$-ethenoadenine, 3,$N^4$-ethenocytosine and 7-*N*-(2-oxoethyl)guanine[8]. 1,$N^6$-Ethenoadenine and 3,$N^4$-ethenocytosine were shown to have miscoding properties for *Escherichia coli* DNA polymerase I[9], but the presence of these adducts in DNA *in vivo* is questioned[8]. Therefore, we have investigated the coding properties of the main adduct, 7-*N*-(2-oxoethyl)guanine, using chloroethylene oxide-treated poly(dG-dC) as template and polymerase I. Templates containing up to 50% 7-*N*-(2-oxoethyl)guanine and 1–5% 3,$N^4$-ethenocytosine (as determined by high-performance liquid chromatographic analysis) were

[6] Khudoley, V., Malaveille, C. & Bartsch, H. (1981) *Cancer Res.*, **41**, 3205–3210.
[7] Malaveille, C., Croisy, A., Brun, G. & Bartsch, H. (1983) *Carcinogenesis* (in press).
[8] Laib, R. J., Gwinner, L. M. & Bolt, H. M. (1981) *Chem.-biol. Interact.*, **37**, 219–231.
[9] Barbin, A., Bartsch, H., Leconte, P. & Radman, M. (1981) *Nucleic Acids Res.*, **9**, 375–387.

replicated in the presence of complementary and non-complementary nucleotides and submitted to 'nearest neighbour' analysis. The effect of 'nicking' apyrimidinic/apurinic sites on the misincorporation rates was also investigated. It was observed that most of the miscoding errors were due to apyrimidinic sites and other unidentified deoxycytidine lesions; from this observation, GC→AT transitions were predicted. 7-*N*-(2-Oxoethyl)guanine had essentially the coding properties of guanine, eliminating a previous hypothesis that this DNA adduct could be a promutagenic lesion of vinyl chloride[10]. Together with previous reports[11], our results indicate that the three known vinyl chloride-DNA adducts and their secondary lesions can alter the fidelity and process of replication.

Chloroethylene oxide is a 'missense' mutagen in bacteria. The types of base-pair substitutions induced by this compound in *E. coli* were investigated, using the tryptophan synthetase A system developed by Yanofsky[11]. Seven trp$^-$ mutant strains were treated with four different doses of chloroethylene oxide, and the prototrophs were characterized biochemically. Dose-response curves showed that GC→AT transitions and AT↔TA transversions were induced at frequencies 20 and three times higher, respectively, than the frequencies of the other base-pair substitutions. Although the number of mutant sites investigated was limited, these data correlate well with the predictions made from the misincorporation assays. Therefore, like methylating and ethylating agents, chloroethylene oxide (vinyl chloride) induces mainly GC→AT transitions; however, the main promutagenic lesion appears to be not an $O^6$-alkylguanine but an apyrimidinic site.

Studies have been initiated to prepare specific antibodies against vinyl chloride-DNA adducts. Antisera against 1,$N^6$-ethenodeoxyadenosine and 3,$N^4$-ethenodeoxycytidine were obtained from rats and mice immunized with nucleoside-protein conjugates; a high-affinity constant, $6 \times 10^8$ L/mol, was observed with an anti-ethenodeoxyadenosine rat serum. In order to obtain monoclonal antibodies, spleen cells from immunized animals were fused to myeloma cell lines, and the cultures were tested for the presence of specific antibodies by radioimmunoassay or enzyme-linked immunosorbent assay; attempts to isolate positive clones have so far been unsuccessful. Immunization of rodents against 7-*N*-(2-oxoethyl)guanine, using nucleoside-protein conjugates or synthetic polynucleotides, gave negative results, possibly because of the chemical and/or enzymic degradation of the oxoethylguanine derivatives.

(*b*) *Influence of age on induction of preneoplastic foci and on alkylation of rat liver DNA by vinyl chloride* (Miss R. Cartier; in collaboration with Dr R. J. Laib and Dr H. M. Bolt, Institute of Pharmacology, Toxicology Unit, University of Mainz, FRG)

The hepatocarcinogenesis of vinyl chloride is a striking example of the influence of age on the neoplastic response: subchronic exposure of newborn rats results in angiosarcomas and hepatocellular tumours at about the same incidence, whereas the same exposure of older (13 weeks) animals has no effect on the liver[12]. The age-dependence of liver susceptibility was investigated in rats exposed to vinyl chloride for various time intervals and at different periods after birth by evaluating preneoplastic hepatocellular foci with ATPase (nucleoside-5'-triphophatase) deficiency.

[10] Scherer, E., Van der Laken, G. J., Gwinner, L. M., Laib, R. J. & Emmelot, P. (1981) *Carcinogenesis*, 2, 671–677.
[11] Yanofsky, C., Ito, J. & Horn, V. (1966) *Cold Spring Harbor Symp. Quant. Biol.*, 31, 151–162.
[12] Maltoni, C. (1977) *Environ. Health Perspect.*, 21, 1–5.

The initiation of preneoplastic lesions by vinyl chloride is restricted to a well-defined period in early life (days 7—21). A comparison of the period in which the liver is sensitive to foci initiation with the time course of liver growth reveals that the most sensitive period is followed directly by a steep increase in liver weight.

Exposure of 12-day-old rats and adult animals to $^{14}$C-vinyl chloride and subsequent analysis of liver DNA showed comparable patterns of adducts [7-*N*-(2-oxoethyl)guanine but no etheno-deoxyadenosine or ethenodeoxycytidine]; the young animals showed a six-fold higher level of 7-*N*-(2-oxoethyl)guanine[13]. These results indicate that the high susceptibility of young rats to vinyl chloride-induced liver carcinogenesis may be related to diminished DNA repair during the phase of increased cellular proliferation.

## 3. MECHANISMS OF ACTION OF TUMOUR PROMOTERS

As in past years, phorbol ester-type tumour promoters were used as model compounds to study the mechanism of action of such compounds. More studies on the interaction of tumour promoters with the cellular membrane were carried out this year, since it had become apparent that this plays a key role.

(*a*) *Characterization of a human placental factor which inhibits specific binding of phorbol esters* (Dr H. Yamasaki, Miss E. Hamel and Miss N. Martel; in collaboration with Dr J. L. Tayot, Institut Mérieux, Marcy l'Etoile, France)

It is now well documented that tumour promoting phorbol esters bind to a variety of cells through specific high-affinity receptors[14]. In an attempt to find the putative endogenous ligand(s) for the receptor, we used the human placenta as a possible source. We have partially purified a phorbol ester binding inhibitory factor (PEBIF) which can inhibit the binding of [$^3$H]-phorbol-12,13-dibutyrate ($^3$H-PDBu) on different types of cells, by alcohol fractionation, CM Sephadex chromatography, Con A Sepharose affinity chromatography and Sephadex G 100 filtration. PEBIF did not lose its inhibitory activity after heating, acid treatment (pH 3) or precipitation with 80% alcohol.

PEBIF inhibits binding of $^3$H-PDBu to human amniotic membrane cells, murine erythroleukaemia cells and rat liver epithelial cells in culture. The inhibition was seen at both 37°C and 4°C and was reversible. In most cases, PEBIF inhibits $^3$H-PDBu binding in a non-competitive manner, but a competitive inhibition was observed with two lines of rat liver epithelial cells. The reason for this difference is not clear.

In order to see whether PEBIF acts as an agonist or an antagonist of 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA), several of its biological effects were examined. TPA and PEBIF were found to share two effects: inhibition of terminal differentiation of TPA-sensitive clones and not TPA-resistant clones in Friend erythroleukaemia cells and stimulation of uptake of 2-deoxy-glucose in BALB/3T3 cells. PEBIF, however, failed to mimic three other TPA effects: EB virus

[13] Laib, R. J., Cartier, R., Bartsch, H. & Bolt, H. M. (1983) *Cancer Res. clin. Oncol.*, **105**, A21.

[14] Blumberg, P. M., Delclos, K. B., Dunphy, W. G. & Jaken, S. (1982) In: Hecker, E., Fusenig, N. E., Kunz, W., Marks, F. & Thielmann, H. W., eds. *Cocarcinogenesis and Biological effects of Tumor Promoters*, New York, Raven Press, pp. 519–535.

induction in a lymphoblastoid cell line Raji, inhibition of cell-cell communication and induction of differentiation of human promyelocytic leukaemia cells (HL 60).

Recently, it has been shown that the specific binding sites of phorbol esters may consist of a calcium- and phospholipid-dependent protein kinase (protein kinase C)[15, 16]. TPA and related tumour promoters activate this kinase *in vitro*. When PEBIF was included in an assay mixture with protein kinase C, an inhibition rather than an activation was observed. Further studies to examine the relationship between PEBIF and protein kinase C are under way.

(*b*) *Inhibition of intercellular communication by tumour promoters* (Mr T. Enomoto and Dr H. Yamasaki)

We demonstrated previously that tumour promoting phorbol esters reversibly inhibit electrical coupling (ionic transfer) between cultured cells[17, 18]. Since accurate measurement of electrical coupling can be done only in paired cells and not in confluent culture, and since electrical measurement is extremely laborious, we decided to use another means to measure intercellular communication—the 'dye transfer' method. In this method, fluorescent dye (e.g., Lucifer Yellow CH) is microinjected directly into individual cells under a microscope, using an Olympus injectoscope[19].

With the dye transfer method we could also demonstrate reversible inhibition of intercellular communication of cultured cells. Almost complete inhibition of intercellular transfer of fluorescent molecules between cells was observed with BALB/3T3 cells and Chinese hamster V79 cells. A typical effect of TPA is shown in Fig. 8 (C, D). This method should prove useful for studying the mechanism by which tumour promoters inhibit intercellular communication.

During our search for inhibitors of phorbol ester-mediated inhibition of intercellular communication, we found that dbcAMP together with phosphodiesterase inhibitors (aminophylline and caffeine) can protect against the effect of TPA (Fig. 8 G, H). This is consistent with the recent finding that cAMP is an endogenous up-regulating factor in intercellular communication[20].

(*c*) *Membrane effect of phorbol esters in cultured rat liver epithelial cells* (Dr H. Yamasaki, Dr A. V. Lyubimov and Miss N. Martel)

Treatment with TPA results in the formation of strand-like aggregates (ridges) of viable cells over the monolayer of IAR 6-1 cells[21] but not of three other cell lines tested (IAR 20, IAR 6, IAR 6–7). To elucidate the mechanisms of the morphological response of IAR 6-1 to TPA, we used various means, including determination of phorbol ester receptors, analysis of cellular fucoproteins, surface galactoproteins and iodinatable surface proteins, as well as specific immunofluorescence for several defined components of the extracellular matrix (fibronectin, laminin-entactin, procollagen type III).

A class of specific and saturable receptors for phorbol esters with high affinity was demonstrated in all four cell lines employing a conventional $^3$H-PDBu binding assay. The dissociation

[15] Castagna, M., Takai, Y., Kaibuchi, K., Sano, K., Kikkawa, U. & Nishizuka, Y. (1982) *J. biol. Chem.*, **257**, 7847–7851.
[16] Ashendel, C. L., Staller, J. M. & Boutwell, R. K. (1983) *Biochem. biophys. Res. Commun.*, **111**, 340–345.
[17] Enomoto, T., Sasaki, Y., Shiba, Y., Kanno, Y. & Yamasaki, H. (1981) *Proc. natl Acad. Sci. USA*, **78**, 5628–5632.
[18] Yamasaki, H., Enomoto, T., Martel, N., Shiba, Y. & Kanno, Y. (1983) *Exp. Cell Res.*, **146**, 297–308.
[19] Yamamoto, F. & Furusawa, M. (1978) *Exp. Cell Res.*, **117**, 441–445.
[20] Flagg-Newton, J. L., Dahl, G. & Loewenstein, W. R. (1981) *J. Membrane Biol.*, **63**, 105-121.
[21] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 90.

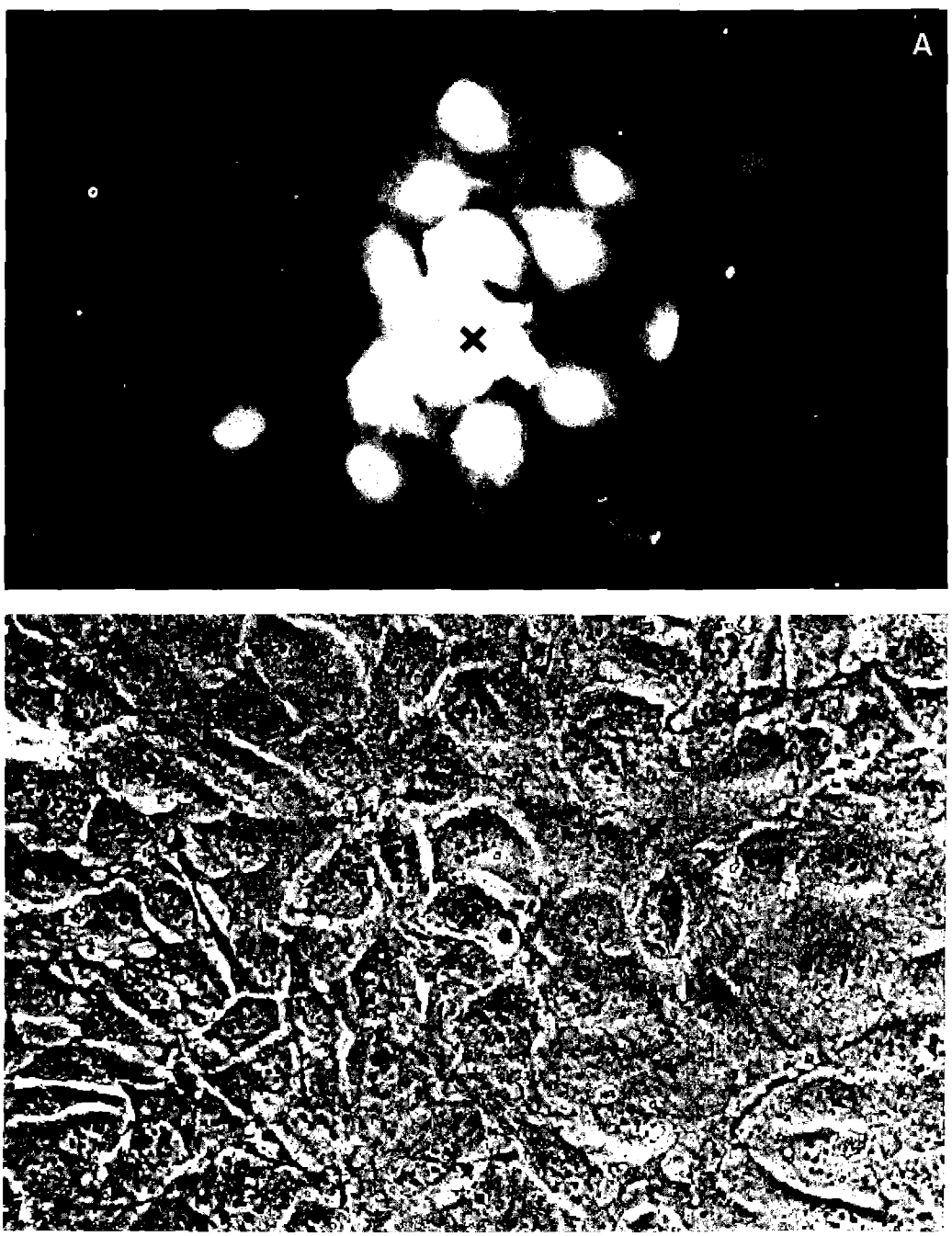
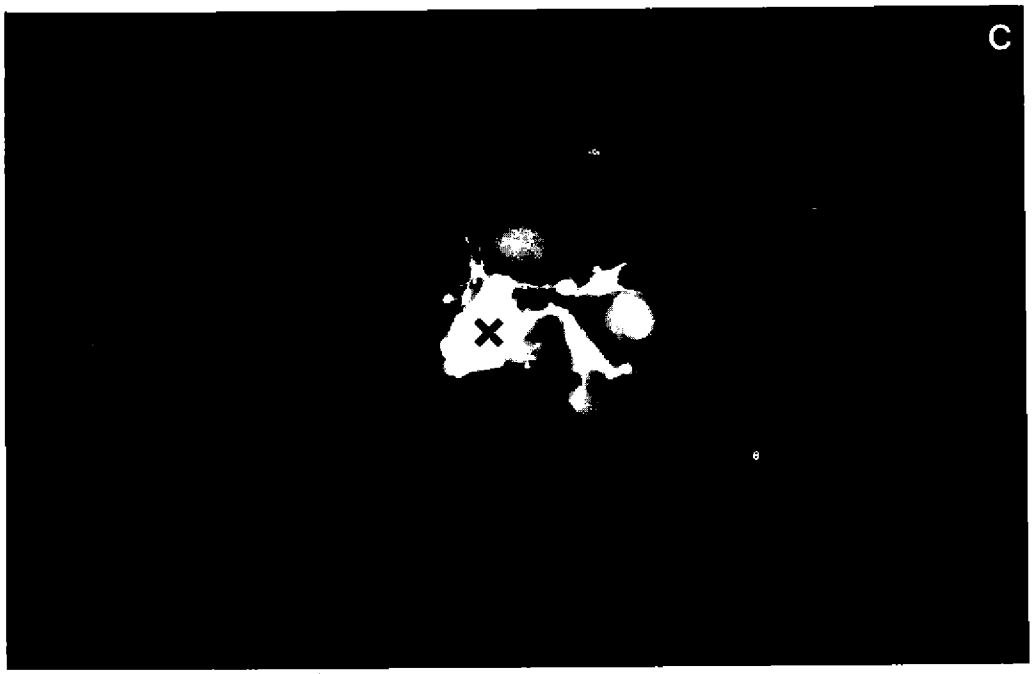



Fig. 8 Effects of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and cAMP on intercellular communication measured by fluorescent dye transfer between BALB/3T3 cells. A, B, control culture; C, D, culture treated with 100 ng TPA for 8 h; E, F, culture treated with 1 mmol/L dbcAMP and 1 mmol/L caffeine for 8h; G, H, culture treated with TPA, dbcAMP and caffeine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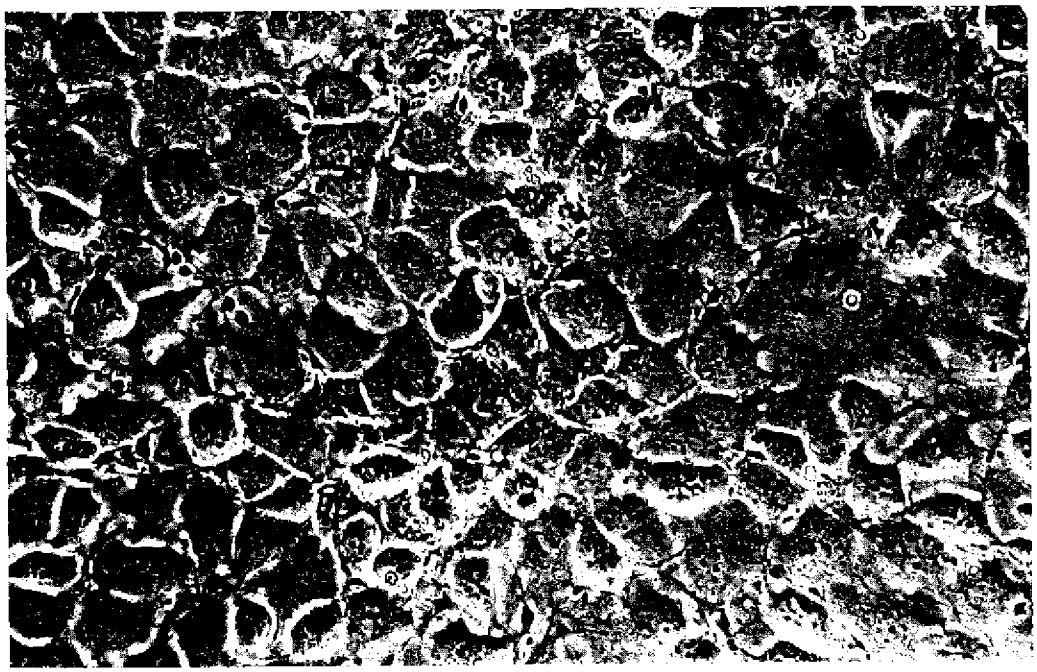

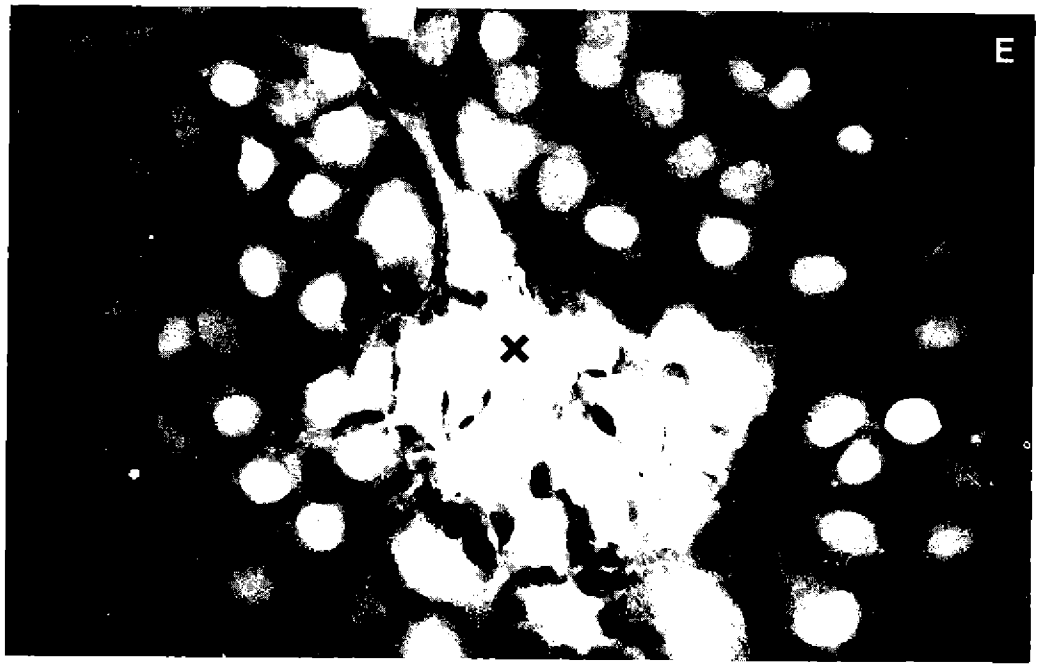
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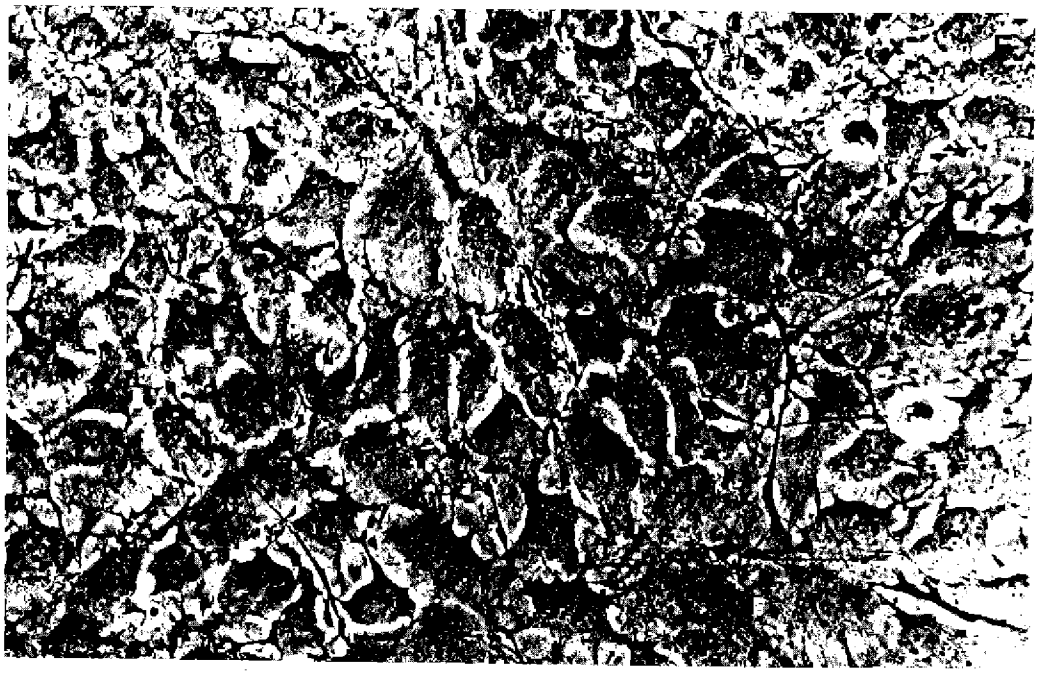

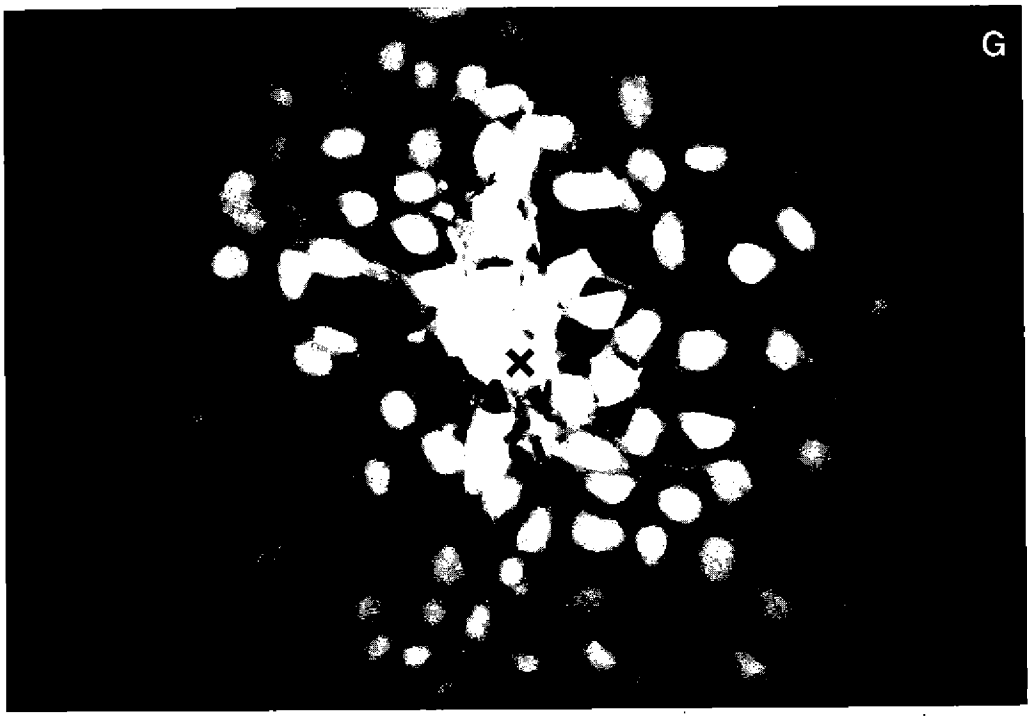
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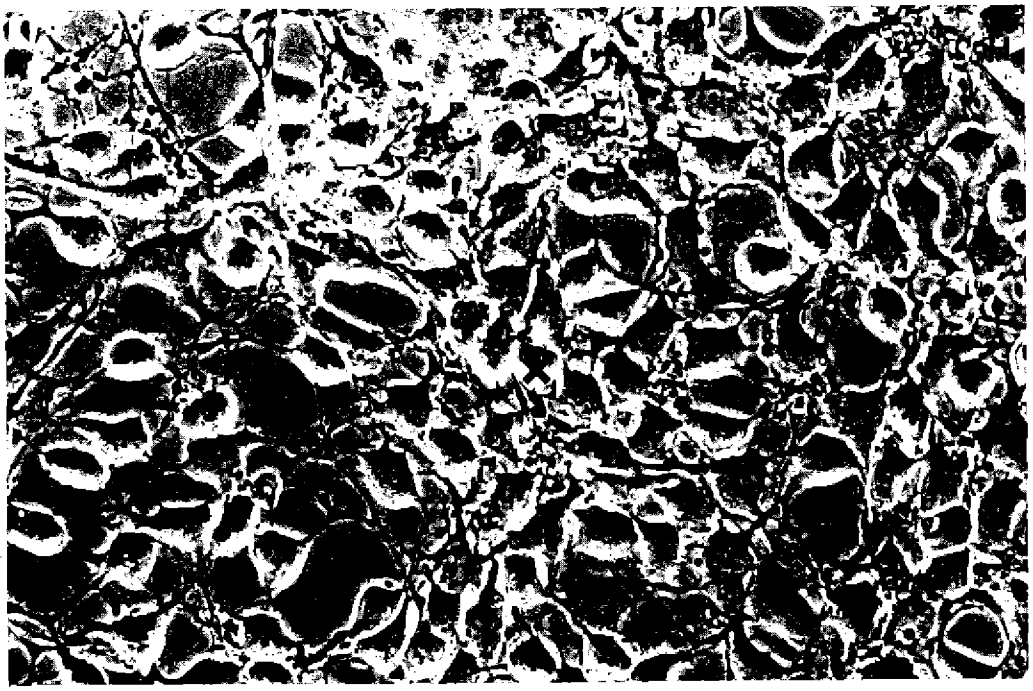

constants were similar in the cell lines studied, while the number of receptors per cell in IAR 6-1 cells was about double that in other lines. Iodinatable surface proteins and galactose-containing surface glycoproteins showed no response to TPA, nor was any significant difference in the patterns of these components between cell lines detected. Distribution of fibronectin, laminin-entactin and procollagen type III was not affected by TPA. The TPA-responsive cell line, IAR 6-1, contained considerably less laminin-entactin than other lines. TPA had no influence on metabolic labelling of [$^3$H]-fucose-containing cellular glycoprotein in IAR 6-1 cells. One specific protein, 77.5 KD, was more heavily labelled with [$^3$H]-fucose in IAR 6-1 cells than in other cell lines.

These results show that, despite the presence of a class of high affinity binding sites for phorbol esters, TPA does not affect various membrane parameters of cultured rat liver epithelial cell lines, except for morphological changes in one cell line, IAR 6-1. The responsive cells differed from nonresponsive ones in having an increased number of specific phorbol ester receptors, an increased fucosylation of a specific glycoprotein and a decreased deposition of laminin-entactin into the extracellular matrix. These surface properties of IAR 6-1 cells may contribute to their ability to respond to TPA.

(*d*) *Two-stage in-vitro cell transformation* (Dr H. Yamasaki and Mrs A. M. Aguelon; in collaboration with Dr T. Kakunaga, National Cancer Institute, Bethesda, MD, USA)

Our effort to establish a two-stage model of in-vitro cell transformation is being continued, using BALB/3T3 clone 13-1-1. When cells were treated with 3-methylcholanthrene (MCA, 0.1 μg/ml) and then with TPA, mezerein or 12-*O*-retinoyl phorbol 13-acetate (RPA), the relative potencies in promoting cell transformation were in the order mezerein > TPA > RPA. The dose-response to mezerein of in-vitro promotion of cell transformation is shown in Fig. 9A. The reason for the lower activity of a potent mouse skin tumour promoter in in-vitro cell transformation is not clear, but it has been suggested recently that the metabolic inactivation of TPA may represent a partial explanation[22].

After initiation of cell transformation with MCA, continuous treatment with mezerein for at least three weeks was necessary to obtain a maximum increase in cell transformation. When the treatment was discontinued after two weeks, only 20% of the yield of cell transformation was obtained after three weeks or more of treatment time (Fig. 9B). This in-vitro system should be useful for studying cellular mechanisms of tumour promotion.

(*e*) *In-vivo two-stage carcinogenesis* (Dr H. Yamasaki, Dr J. R. P. Cabral, Mrs D. Galendo and Dr L. Tomatis)

In order to examine whether phorbol esters promote internal organ tumorigenesis as well as skin tumorigenesis, a transplacental initiation-postnatal promotion experiment was carried out in C57BL/6 mice. Mice were initated transplacentally with benzo[*a*]pyrene, and newborn mice were treated with TPA by either painting on the skin of the back or intraperitoneal injection. No promoting effect of TPA was observed in any organ. Since it is recognized that C57BL/6 mice are relatively resistant to initiation-promotion tumorigenesis, a new set of experiments with CD-1 mice is now under way.

[22] Hirakawa, T., Kakunaga, T., Fujiki, H. & Sugimura, T. (1982) *Science*, **216**, 527–529.

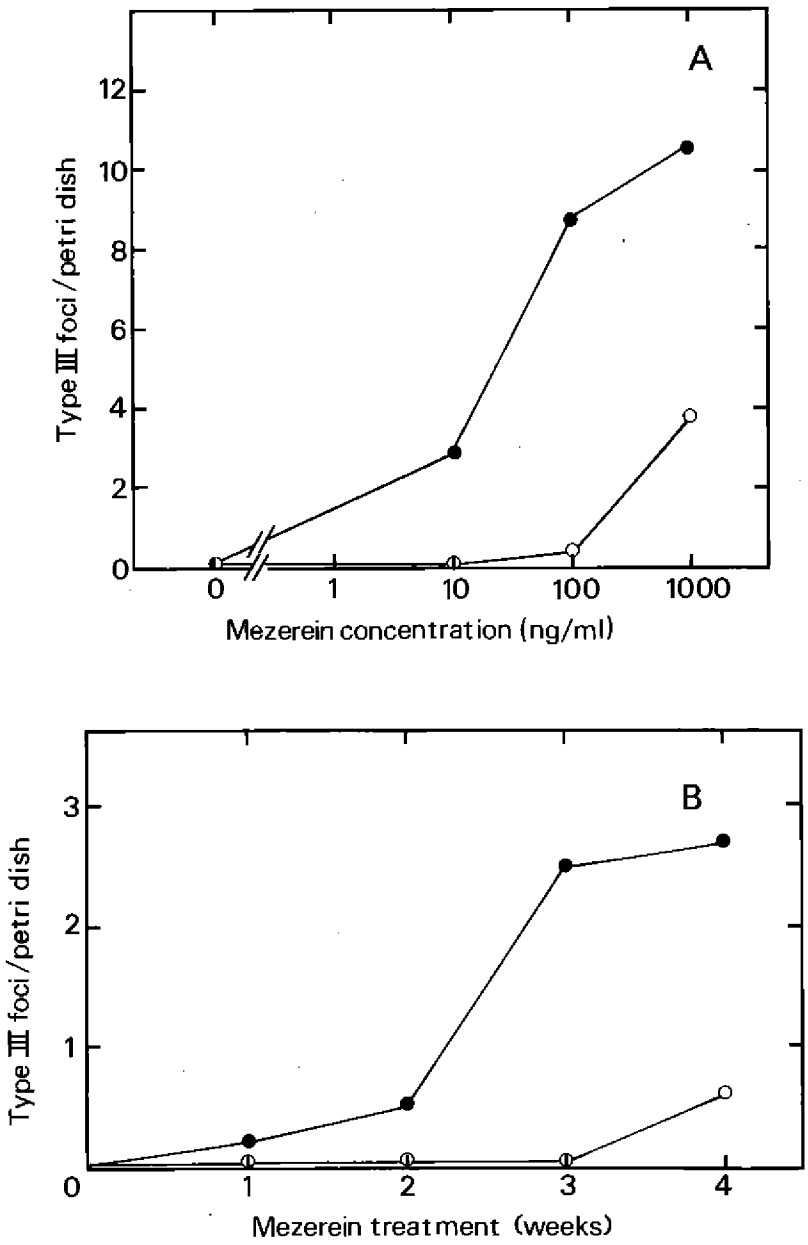


Fig. 9. Two-stage in-vitro transformation of BALB/3T3 cells. A, Dose-response to mezerein treatment with (●) and without (○) initiation of cell transformation by MCA; B, effect of duration of mezerein treatment on cell transformation.

(*f*) *Quantitative effects of tumour initiator and promoters* (Dr H. Yamasaki, Dr J. R. P. Cabral, Dr N. E. Day, Dr J. Wahrendorf and Mrs D. Galendo; in collaboration with Dr I. Chouroulinkov, Institut de Recherches Scientifiques sur le Cancer, Villejuif, France)

Quantitative studies of tumour initiation and promotion are scarce[23], yet the existence of a threshold dose for tumour promoters is often discussed. We have initiated experiments to examine the dose-response of an initiator (benzo[*a*]pyrene) with and without a promoter (TPA) in C57BL/6 mice and to determine the quantitative response to tumour promoters in the presence of an initiator in CD-1 mice. In the latter study, various doses of promoter were applied, with various intervals between applications, in order to establish a quantiative dose-time response to the tumour promoter, which is considered to be an important aspect in the estimation of risk of these compounds[23]. These experiments are being carried out by skin painting, and we envisage completion of the experiment by the end of 1984.

(*g*) *Action of phorbol ester tumour promoters on human epidermal cells* (Dr T. Kuroki, Institute of Medical Science, Unviersity of Tokyo; DEC/79/006)

The capacity of human epidermal cells in culture to metabolize benzo[*a*]pyrene and the variation that exists among species, individuals and cell types has been investigated[24, 25]. More recently, the action of TPA and related compounds on these cells was examined and was compared with the various pleiotropic effects of TPA in other cell types[26]. The binding of phorbol esters to human epidermal cells appears unique, in that there is a large number of binding sites as compared with mouse epidermal cells, and there is no down-regulation. The functional significance of the presence of the binding sites was further investigated by examining the biological responses of these cells to TPA and other tumour promoters.

In human epidermal cells, TPA inhibits DNA synthesis and uptake of 2-deoxy-D-glucose, a sugar analogue, and does not result in induction of ornithine decarboxylase. Teleocidin B, a tumour promoter structurally unrelated to TPA but with ornithine decarboxylate inducibility in mouse skin similar to that of TPA, also failed to induce ornithine decarboxylase activity in human epidermal cells.

Mouse epidermal cells reacted differently from human epidermal cells on addition of TPA, resulting in stimulation of DNA synthesis, sugar uptake and polyamine synthesis. Stimulation of these three reactions appears to be associated with down-regulation of binding sites for phorbol esters rather than to the amounts bound.

(*h*) *Role of cocarcinogens and promoters in human and experimental carcinogenesis, Budapest, 16-18 May 1983* (Dr W. Davis, Dr N. E. Day and Dr H. Yamasaki, in collaboration with Dr M. Börzsönyi, National Institute of Hygiene, Budapest)

The symposium, organized in Budapest by the Hungarian Cancer Society with the support of the Agency and the sponsorship of the European Association for Cancer Research, brought

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[23] Yamasaki, H. & Weinstein, I. B. (1983) In: *Proceedings of SGOMSEC Workshop on Quantitative Estimation of Risk to Human Health from Chemicals*, New York, Wiley (in press).

[24] Kuroki, T., Nemoto, N. & Kitano, Y. (1980) *Carcinogenesis*, **1**, 559–565.

[25] Kuroki, T., Hosomi, J., Munakata, K., Onizuka, T., Terauchi, M. & Nemoto, M. (1982) *Cancer Res.*, **42**, 1859–1865.

[26] Chida, K. & Kuroki, T. (1983) *Cancer Res.*, **43**, 3638–3642.

together 102 scientists from 17 countries. The aim of the meeting, which had developed from a symposium held in 1980, was to bring together experimentalists and epidemiologists, since each group approaches the problems of cocarcinogenesis and promotion in a quite different way.

The papers and posters presented at the meeting gave evidence of substantial advances made in the field in the recent period. They will be published as *IARC Scientific Publications* No. 56.

## 4. CHEMICAL CARCINOGENESIS AND MUTAGENESIS IN CULTURED CELLS

(*a*) *Mutagenesis and transformation in BALB/3T3 cells* (Dr H. Yamasaki, Mrs C. Piccoli and Dr K. Fujie; in collaboration with Dr T. Kakunaga, National Cancer Institute, Bethesda, MD, USA)

At a recent ad-hoc meeting on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, it was concluded that 23 chemicals and groups of chemicals are causally associated with cancer in humans[27]. When the results obtained from a variety of short-term tests are summarized, it became evident that not all of these 23 human carcinogens are positive in the tests which measure genetic activity[27].

In order to detect both genetic and non-genetic activity of chemicals, we are developing a system in which mutation and transformation can be measured in the same cells. Using BALB/3T3 cells and 3-methylcholanthrane and *N*-methyl-*N*-nitrosourea as positive control chemicals, we have optimized the conditions for cell transformation and mutation, as shown in Figure 10. With

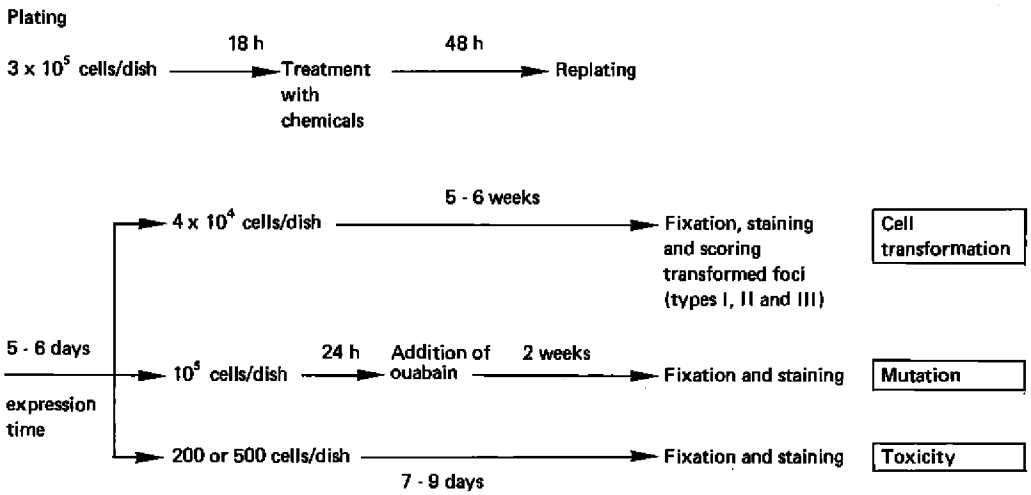


Fig. 10. Procedures for measuring mutation and transformation with BALB/3T3 cells.

[27] International Agency for Research on Cancer (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 4, *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29)*, Lyon.

this system, we are testing diethylstilboesterol and benzene for their activity in mutation and cell transformation. The chemicals that we plan to test in this system include DDT, ethylene thiourea, 1,4-dioxane, γ-hexachlorocyclohexane and methoxychlor.

(*b*) *Cellular and biochemical markers of neoplastic transformation of epithelial cells in culture* (Dr J. M. Vasiliev, Cancer Research Center of the USSR Academy of Medical Sciences, Moscow; DEC/79/010)

Studies were continued to further characterize neoplastic and non-neoplastic IAR cells, primarily by investigating intermediate filaments of the cytoskeleton that are tissue-specific, to elucidate the origin of IAR cells, as well as to probe the molecular mechanisms underlying alterations of cell morphology following neoplastic transformation[28].

The technique of monoclonal antibody production was applied to obtain clones that secrete specific antibodies against protein constituents of rat liver intermediate filaments. One clone made antiprekeratin antibodies, specific for epithelial cells; another produced antivimentin antibodies, specific for mesenchymal cells; and a third produced antibodies that recognize a common antigenic determinant on prekeratin and vimentin. It was shown by immunofluorescence and immunoblotting that, unlike hepatocytes, IAR cells contain only vimentin. Intermediate filaments in non-tumorigenic IAR cells co-distributed with microtubules; this co-distribution was altered in tumorigenic cells, suggesting that neoplastic transformation causes changes in the cytoskeleton of IAR cells.

Study of γ-glutamyltranspeptidase, the only epithelial marker enzyme found in IAR cells, showed that its expression is dependent inversely on the degree of cell spreading on the substratum. These data suggest that the expression of this enzyme in neoplastic cells is due to alterations in their interactions with the substratum.

(*c*) *Role of carcinogenic agents in determining tumour growth rate and metastatic potential* (Dr S. Plesnicar and Dr G. Sersa, Institute of Oncology and Faculty of Medicine, Ljubljana, Yugoslavia; DEC/83/002)

The specific aim of this investigation is to test to what extent the grade of malignancy of an induced tumour is determined by the type of carcinogenic agent used. The biological characteristics of mammary tumours induced by different carcinogens will be investigated in a mouse model. Specifically, the grade of malignancy will be studied by determining the rate of growth of the induced mammary tumours by doubling determinations of time values, by observing the time lapse from the appearance of the primary tumours to the appearance of distant metastases, and by studying the rate of growth of pulmonary metastases.

(*d*) *Mutagenesis of a bacterial gene, ECo*gpt, *in human cells* (Dr C. Drevon, Dr C. F. Arlett, Dr J. F. Burke and Dr M. R. James, MRC Cell Mutation Unit, University of Sussex, Falmer, Brighton, UK; DEC/82/021)

The alterations induced by ultra-violet and γ rays in the structure of a small bacterial gene which has been indroduced into human cells have been studied using a SV40 pBR322 recombinant

[28] Bannikov, G. A., Guelstein, V. I., Montesano, R., Tint, I. S., Tomatis, L., Troyanovsky, S. M. & Vasiliev, J. M. (1982) *J. Cell Sci.*, **54**, 47–67.

(pSV2) which contains the *Escherichia coli* sequence ECo*gpt*, coding for XPRT, the bacterial analogue of the mammalian enzyme HGPRT. Human skin fibroblasts deficient in HGPRT have been transfected by the calcium phosphate precipitation technique with different concentrations of the plasmid in the presence and in the absence of carrier DNA, in order to obtain a clone containing only one copy of the bacterial gene. In some experimental groups, the transfection was performed with pSV2*gpt* ligated to $\pi\delta$ *lac*, a plasmid containing a suppressor of amber mutations, which will be helpful in future investigations when the mutated ECo*gpt* genes have been rescued and sequenced.

So far, more than 20 *gpt*$^+$ transformants have been isolated, after selection in an appropriate medium and the number of copies of the *gpt* gene per cell in each of these clones is presently under investigation using the Southern blot technique. The phenotypic and genotypic stability of these clones is also being investigated.

(*e*) *Investigation of an in-vitro assay for measuring genetic changes in mammalian cells* (Dr M. Radman and Ms G. Maenhaut, Department of Molecular Biology, University Libre, Brussels; DEC/82/016)

A new, highly sensitive, well defined method is being developed to measure genetic changes in human and other cells both *in vivo* and *in vitro*. The genetic alterations that we intend to detect are changes in DNA nucleotide sequence (single base-pair substitutions and frameshift mutations) in either somatic or germ line cells. The method is based upon properties of enzymes that can recognize mismatched base pairs or mismatched regions in reannealed DNA.

Mismatched base pairs can occur in DNA as the result either of errors in replication (replication heteroduplex) or DNA strand exchange between homologous but non-identical DNA sequences (recombinational heteroduplex), as well as by specific chemical modifications of DNA bases. Replicational heteroduplexes are subject to a highly efficient strand-directed mismatch correction leading to conservation of DNA nucleotide sequences, whereas recombinational heteroduplexes are subject to random mismatch repair leading to diversification of nucleotide sequences. Mismatch repair depends on *mutH, mutL, mutS* and *mutU* genes in *E. coli*.

Our results indicate that the dual role of the mismatch repair system depends on methylation of adenine in GATC sequences: strand methylation prevents repair, thus directing correction on the nonmethylated strand, whereas in the absence of GATC sequences or methylation, mismatch repair can operate randomly. We have developed two different experimental systems to purify mismatch repair enzymes: (1) An in-vitro system using heteroduplex DNA of phage $\varnothing \times 174$ (which is devoid of GATC sequences), containing a short (about 60 nucleotides) intergenic insert of pBR322 plasmid DNA with or without GATC sequences and an *amber*/+ mismatch. These substrates are being used to detect mismatch correction *in vitro* and to determine its requirements. (2) A genetic system using a derivative of bacteriophage Mu:d lac Ap (Casadaban) to obtain mut/β-gal protein fusions by insertion of the Mu:d lac Ap phage in the *mutH, mutL, mutS* and *mutU* genes. We have isolated nine different candidates in which the Mu phage seems to be inserted in one of the *mut* genes in the right orientation and reading frame. These will be used for the isolation of fused mut/β-gal 'hybrid' proteins and the purification of mismatch repair enzymes by specific antibody precipitation.

Parallel to the efforts to purify mismatch recognition proteins (*mutH, L,S.* and *U*), a genetic study has been undertaken (using a complete repertoire of base pair mismatches present in heteroduplex λ DNAs), to determine the mismatch recognition specificity of the individual *mut*

proteins *in vivo*. This information is crucial for the use of *mut* proteins in measurements of DNA sequence divergence.

## 5. ROLE OF CYTOGENETIC ANOMALIES IN THE ETIOLOGY OF HUMAN CANCER

(*a*) *Epstein-Barr virus serology* (Dr G. Lenoir and Mrs M. F. Lavoué; in collaboration with Professor J. Daillie, Alexis Carrel Faculty of Medicine, Lyon, France; DEC/81/026)

Serological investigations have been continued in order to support the programme on BL. Studies for evaluating the immune response to EBV-infected cells in patients with various diseases, including infectious mononucleosis, primary and secondary immunodeficiencies[29] and leukaemias, have been performed to identify biological factors involved in the control of EBV infections.

(*b*) *Cell cultures of Burkitt-type lymphomas* (Dr G. Lenoir, Mrs M. Vuillaume, Mrs S. Pauly and Mrs I. Philip)

The majority of Burkitt-type lymphomas can be cultivated *in vitro* as continuous lymphomatous cell lines, independent of the presence of the EBV genome. Moreover, normal 'non-malignant' human B lymphocytes can also be cultivated *in vitro* continuously, once they have been 'immortalized' by EBV. Taking advantage of these two facts, transformation of human lymphocytes is being studied. Seventy new BL lines derived from cases originating in low-incidence areas have been established, 14 from EBV-free lymphomas. This is the largest collection of malignant BL lymphoma lines presently available. The cells are being used in collaborative studies of the phenotype, the genotype and the cytogenetic characteristics of BL cells (see below), e.g., to characterize a monoclonal antibody with anti-BL specificity[30]. In collaboration with the group of J. C. Dreyfus (Institute of Molecular Pathology, Paris), we have shown that elevated glycohydrolase activity may be a possible enzymatic marker for malignancy in BL cells[31]. Thorough cytological and immunological investigations are also being performed on this material.

(*c*) *Cytogenetic investigations on lymphoid cells* (Mrs E. Mark-Vendel and Mrs O. Maritaz; in collaboration with Dr R. Berger, Institute for Research on Blood Disorders, Paris; and Dr J. Fraisse, Blood Transfusion Centre, St Etienne, France)

These studies represent one of the main activities of the group during the past year. They have indicated that, independent of the geographic origin of the patient, the association with EBV and the clinical presentation, BL cells always carry one of the following translocations: t(8;14), t(2;8) or t(8;22). Our study, performed on African and North African cases, clearly showed that the variant translocations t(2;8) and t(8;22) are not limited to non-endemic European or Japanese cases[32]. All of the BL cases studied in the framework of this programme had one of the specific translocations, and a relative proportion of the three types of translocations can be estimated (Table 16).

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[29] Vilmer, E., Lenoir, G. M., Virelizier, J. L. & Griscelli, C. (1983) *Clin. exp. Immunol.* (in press).

[30] Wiels, J., Lenoir, G. M., Fellous, M., Lipinski, M., Salomon, J. C., Tetaud, C. & Tursz, T. (1982) *Int. J. Cancer*, **29**, 653–658.

[31] Skala, H., Lenoir, G. M., Pichard, A. L., Vuillaume, M. & Dreyfus, J. C. (1982) *Blood*, **60**, 912–917.

[32] Bernheim, A., Berger, R. & Lenoir, G. (1981) *Cancer Genet. Cytogenet.*, **3**, 307–315.

Table 16. Estimations of the proportion of the various types of specific translocations found in Burkitt-type lymphoma, based on an analysis of 50 cases

| Translocation | No. of cases | Percentage |
|---|---|---|
| t(8;14) | 36 | 72% |
| t(2;8) | 4 | 8% |
| t(8;22) | 10 | 20% |

Chromosomes 14, 2 and 22 have been shown recently to carry genes for immunoglobulin heavy chains and for light chains kappa and lambda, respectively. Our study on the correlation between Ig light chain expression and variant translocation in BL[33] strongly suggests that malignant transformation may result from transposition of a segment of chromosome 8 (8q24) to an active region of an Ig-locus-carrying chromosome. This situation is very similar to that observed in animal plasmacytomas and suggests that BL can be used as a human model for studying the role of genetic transposition in carcinogenesis (see below).

Secondary chromosomal changes frequently involving chromosome 1 were also detected[34]. Their biological significance is being investigated.

In order to study the mechanism by which translocation can occur in lymphoid cells, a model has been developed using lymphoid cell lines from patients with ataxia telangiectasia. A cell clone carrying a 14q+ marker has been obtained and is being characterized.

(*d*) *Molecular studies on Burkitt's lymphoma cells* (in collaboration with Dr P. Leder, Harvard Medical School, Boston, MA, USA; and Dr G. Bornkamm, Institut für Virologie im Zentrum für Hygiene, Freiburg, FRG)

Following the suggestion[35] regarding the presence on chromosome 8(q24) of DNA sequences involved in cell proliferation, molecular studies have indicated that this segment of chromosome 8 carries one of the known oncogenes, designated 'myc'[36]. Analysis of the BL lines has also indicated that, following the chromosome translocation, this gene comes into the close vicinity of the immunoglobulin genes. A mechanism of 'activation' of an oncogene can thus be studied for the first time at the molecular level in humans, using BL cells.

(*e*) *Chromosomal studies on Ewing's sarcoma cells* (in collaboration with Mrs C. Turc, CHU Faculty of Medicine, Dijon, France; and Dr T. Philip, Centre Léon-Bérard, Lyon, France)

In order to investigate whether genetic transposition also occurs in conditions other than haematopoietic disorders, in which several specific chromosome translocations have been reported, other childhood malignancies have been studied. Cell lines have been established from Ewing's sarcomas, and our study[37] indicated that a translocation t(11;22) (q24,q12) might be a

[33] Lenoir, G. M., Preud'homme, J. L., Bernheim, A. & Berger, R. (1982) *Nature*, **298**, 474–476.
[34] Bernheim, A., Berger, R. & Lenoir, G. (1983) *Cancer Genet. Cytogenet.*, **8**, 223–229.
[35] Klein, G. & Lenoir, G. (1982) *Adv. Cancer Res.*, **37**, 381–387.
[36] Taub, R., Kirsch, I., Morton, C., Lenoir, G., Swan, D., Tronick, S., Aaronson, S. & Leder, P. (1982) *Proc. natl Acad. Sci. USA*, **79**, 7837–7841.
[37] Turc-Carel, C., Philip, I., Berger, M. P., Philip, T. & Lenoir, G. M. (1983) *New Engl. J. Med.* (in press).

characteristic feature of these malignant cells (Fig. 11). The presence of a cellular oncogene, C-sis, on chromosome 22 (q24) suggests that further investigations should be done on this cancer and that genetic transposition, through chromosomal translocation, is not limited to haematopoietic malignancies.

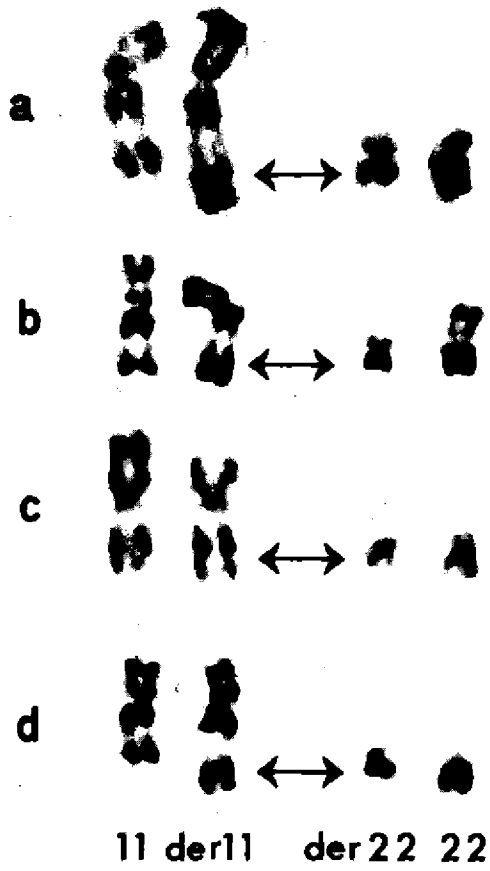


Fig. 11. Partial karyotypes showing the reciprocal translocation (11;22) (q24;q12) in four Ewing's sarcoma cell lines. a, b, d: R-banding from lines IARC-EW 1, IARC-EW 2 and IARC-EW 11; c: G-banding cell IARC-EW 7. Asterisks indicate other anomalies on non-derivative chromosomes.

(*f*) *Relationship between karyotypic pattern of cancer cells and etiological factors* (Dr F. Mitelman, Department of Clinical Genetics, University of Lund, Sweden; DEC/78/013)

Detailed karyotypic data on chromosomal aberrations, as identified by banding techniques, have been collected systematically as a registry since 1970. The material has been collected from

three main sources: published cases ascertained from three separate computer-based literature scans, unpublished cases from our laboratory and unpublished cases kindly communicated by numerous colleagues all over the world. By 1980, the complexity of the information prompted adoption of computer methods for assembling, revising and indexing.

A total of 3877 cases is now contained in the registry. The computerized data are coded for a number of parameters:

detailed morphological diagnosis, tumour site, clinical state and survival;
karyotype, type of tissue studied, technique used for chromosome preparation, and time of culture;
mode of ascertainement, i.e., whether or not the case belongs to an unselected consecutive series of patients studied in a laboratory;
age, sex, ethnic group and geographic region;
previous neoplasm—morphologic diagnosis, topography and type of treatment used;
hereditary disorder, including constitutional chromosomal aberrations in the patient or in relatives;
obvious environmental or occupational exposure to potential mutagenic or carcinogenic agents.

All this information can easily be retrieved and used for scientific purposes. Active workers in the field may, upon request, obtain information directly from Dr Mitelman.

6. PERINATAL CARCINOGENESIS (Dr A. Likhachev, Dr J. R. P. Cabral, Dr L. Tomatis, Mrs D. Galendo and Miss M. Collard; in collaboration with Dr N. P. Napalkov, N. N. Petrov Research Institute of Oncology, Leningrad, USSR, DEC/81/033; and Dr B. N. Hemsworth, Life Science Laboratory, Teeside Polytechnic, Cleveland, UK; DEC/82/001)

Experiments designed to study the possibility that exposure of female rats to *N*-ethyl-*N*-nitrosourea during pregnancy results in an increased cancer risk for successive generations have now been completed[38].

Investigations have been initiated to study the effect of postnatal application of various modifying factors on carcinogenesis in two successive generations of rats and mice exposed transplacentally to different carcinogens. Skin applications of 12-*O*-tetradecanoylphorbol-13-acetate to the F1 and F2 descendants of female mice exposed to 7,12-dimethylbenz[*a*]anthracene during gestation resulted in the appearance of skin tumours. Tumours of the nervous system and kidneys developed in most animals exposed *in utero* to *N*-methyl-*N*-nitrosourea, and these tissues possessed a weaker capacity to repair $O^6$-methylguanine in the DNA[39]. In most F1 and F2 descendants exposed further to thyroidectomy or methylthiouracil, tumours developed in the thyroid and some other organs. Persistent oestrus induced postnatally in F1 and F2 rats exposed to 7,12-dimethylbenz[*a*]anthracene or *N*-methyl-*N*-nitrosourea during embryogenesis resulted in an increase in the carcinogenic effect of those agents.

[38] Cabral, J. R. P., Tomatis, L., Likhachev, A. J., Ponomarkov, V. & Euzeby, B. (1983) *Toxicologist*, 3, 34.
[39] Likhachev, A. J., Alexandrov, V. A., Anisimov, V. N., Bespalov, V. G., Korsakov, M. V., Cvsyannikov, A. I., Popovic, I. G., Napalkov, N. P. & Tomatis, L. (1983) *Int. J. Cancer*, 31, 779–784.

Treatment of male rats with *N*-ethyl-*N*-nitrosourea before mating resulted in the appearance of neurogenic tumours in the progeny[40]. An expanded study is in progress in which tumour appearance is being studied in the offspring of male rats and mice treated with *N*-ethyl- or *N*-methyl-*N*-nitrosourea and mated subsequently.

A further study is being made of a possible carcinogenic effect of the thymidine analogue 5-bromodeoxyuridine (BUdR), which produces miscoding and mutagenic effects and persists in the DNA of various rat tissues over long periods[41]. BUdR is being given to pregnant rats, and then to their offspring during the neonatal period. Since previous experiments had shown that BUdR induced kidney lesions and ethyl methane sulphonate produced kidney tumours, combined administration of the two compounds is also being investigated. BUdR was also administered repeatedly to rats during the neonatal period, and the animals were then exposed either to monolateral nephrectomy (males) or to persistent oestrus induced by subcutaneous implantation of the ovary into the tail following bilateral ovariectomy.

## 7. APPROACHES TO CLASSIFYING CHEMICAL CARCINOGENS ACCORDING TO MECHANISM OF ACTION (Ms L. Haroun, Mr J. Wilbourn and Dr H. Vainio; in collaboration with Dr M. Hollstein, University of California, Berkeley, CA, USA)

On 11–15 April 1983, a working group was convened to advise the IARC on the status of recent developments in defining the mechanisms of tumour induction and on subsequent classification of carcinogenic agents by their presumed mechanism of action. Subgroups considered the roles of epidemiology, animal carcinogenesis studies and short-term tests in providing data that could be interpreted in terms of mechanisms of carcinogenesis. The report of the meeting has been published as *IARC Internal Technical Report* No. 83/001.

The basic concept of carcinogenesis as a multi-stage, multi-mechanism process was shared by all three subgroups. Inferences from epidemiological studies are restricted to whether early stages, late stages, or both, are affected by exposure. Data on the administration of carcinogens in different dose-time combinations in animal experiments may indicate whether a given agent has initiating activity, promoting activity, or both. In contrast, short-term tests may be useful in identifying particular mechanisms that may operate at any stage in the process of carcinogenesis. The following terms were used by the three subgroups:

| | |
|---|---|
| Epidemiology: | – early stage |
| | – late stage |
| Animal carcinogenesis: | – initiation |
| | – promotion |
| Short-term tests: | – induction of altered cells |
| | (a) genetic |
| | (b) epigenetic |
| | – selection of altered cells |
| | (a) inhibition of non-altered cells |
| | (b) growth of altered cells |

[40] Tomatis, L., Cabral, J. R. P., Likhachev, A. J. & Ponomarkov, V. I. (1981) *Int. J. Cancer*, **28**, 475–478.
[41] Likhachev, A. J., Tomatis, L. & Margison, G. P. (1983) *Chem.-biol. Interact.*, **46**, 31–38.

It was considered impossible at the present time to interrelate definitively the terms used by each subgroup, because of the differences in the kinds of evidence on which each set of terms is based. For example, the epidemiological distinction between early-*versus* late-stage actions is not based on any of the specific consideration of short-term tests or animal carcinogenesis studies.

In comparing carcinogenesis in animals with the end-points in short-term tests, there is a conceptual correspondence between initiation and induction of altered cells by genetic effects. The large majority of chemicals with initiating activity give positive results in tests for genetic effects. However, the Working Group concluded that evidence of genetic activity does not prove that a chemical is a carcinogen, nor, if it is a carcinogen, that its carcinogenic effect is due to its genetic activity.

Short-term tests for promotion are insufficiently developed to establish their relationship to the properties of known promotors.

Although the Working Group acknowledged the importance of acquiring knowledge on the mechanism of action of carcinogens, it also considered that, at present, no exhaustive or definitive classification of carcinogens according to mechanism could be made.

# IMPROVEMENT OF DATA COLLECTION AND RESEARCH METHODS

## 1. IMPROVEMENT OF EPIDEMIOLOGICAL DATA COLLECTION

### (a) *Cancer registries* (Dr C. S. Muir)

Continued collaboration with cancer registries is essential for the success of the Descriptive Epidemiology programme. Recent major collaborative projects were Volume IV of *Cancer Incidence in Five Continents* (see p. 29) and the survey of malignant melanoma (see p. 60). Association members participated in working parties on multiple tumours (see p. 100) and also contributed to a series of surveys.

#### (i) *International Association of Cancer Registries* (Dr C. S. Muir, Mrs A. Romanoff and Miss S. Whelan; in collaboration with Professor Pelayo Correa, Louisiana Tumor Registry, New Orleans, LA, USA; DEB/73/016)

The Agency continues to provide a secretariat to the Association. Following a meeting of the SEER (Surveillance, Epidemiology and End Results) registries, funded by the National Cancer Institute of the United States (Dr J. Young), at which the operation of the SEER system was reviewed and scientific papers read, the Association held a scientific meeting, attended by 83 persons, in Seattle, USA on 6–8 September 1982. The main theme of the meeting was 'data collection systems'. A wide range of proffered papers dealt with various aspects of registration practices. Superb local arrangements were made by the State of Washington Cancer Registry (Drs D. Thomas and N. Breslow).

The next meeting of the Association will be held at the German Cancer Research Centre in Heidelberg, Federal Republic of Germany, on 1–3 September 1983, on the topic of 'benefits of cancer registration to the cancer patient and society'. The programme committee comprises Professor G. Riotton (Geneva Cancer Registry), Dr O. M. Jensen (Danish Cancer Registry), Professor G. Wagner (Institute for Information, Documentation and Statistics of the German Cancer Research Centre), Dr H. Tulinius (Icelandic Cancer Registry) and Dr C. S. Muir. Local arrangements are being made by Professor G. Wagner.

#### (ii) *Group for the epidemiology and registration of cancer in Latin-tongued countries* (Dr A. J. Tuyns and Mrs J. Nectoux)

As in previous years, the group met on Ascension day and on the Friday thereafter. Upon the invitation of Professor L. Gafa and Dr L. Dardoni, the meeting was held in Ragusa, Sicily. The opening lecture, on animal experimentation and epidemiological research, was given by Professor B. Terracini. During the four working sessions, some 25 papers were presented on methodological and technical subjects and on a series of cancer sites. They included the influence of social class on

incidence of and survival from digestive tract cancer, acute leukaemia of childhood and a case-control study of lip cancer.

(iii) *Legal basis of cancer registration* (Dr C. S. Muir and Mrs E. Démaret)

Following a survey of the legal basis of cancer registration (*IARC Internal Technical Report* 82/003), it became evident that many cancer registries wish to have an internationally accepted code of registry practice in relation to confidentiality. Following consultation with the Health Legislation Unit of the European Regional Office of WHO (Ms G. Pinet), a working party was established to plan an approach to the problem. This comprises, in addition to the IARC and WHO members named above, Dr J. T. P. Bonte, Netherlands Central Bureau of Statistics, Voorburg, The Netherlands; Dr T. Hakulinen, Finnish Cancer Registry, The Institute for Statistical and Epidemiological Cancer Research, Helsinki; and Dr W. Hunter, Commission of the European Communities, Luxembourg.

(*b*) *Computers and cancer registration*

(i) *Survey of computer use in cancer registries* (Dr D. M. Parkin and Mrs E. Démaret; in collaboration with Dr P. Crosignani, National Institute for the Study and Treatment of Tumours, Milan, Italy)

Analysis of this survey was completed and the results were presented at the meeting of the International Association of Cancer Registries in Seattle (see p. 98). A summary of the findings has been published[1].

(ii) *A microcomputer system for cancer registries* (Dr D. M. Parkin)

A microcomputer was purchased in 1982, and the software was developed by Miss R. Goossens and Mr P. Delfosse (University of Namur, Belgium) to provide a system suitable for small cancer registries with no previous access to automated data processing. The objective is to provide a relatively inexpensive system suitable for registries in developing countries. By furnishing a means of coding and checking incoming cancer cases semi-automatically, and the ability to retrieve and analyse the data, both the quality and value of cancer registration should be enhanced. It has become clear that there is a considerable demand for such a facility.

After a period of field testing at the Lausanne Cancer Registry (Dr F. Levi), a prototype system was demonstrated in May 1983. Following further development and testing of the system in the field with appropriate instruction manuals, it will be demonstrated to interested cancer registries.

(*c*) *Classification and nomenclature: standardization*

It is essential that classifications and nomenclatures change to incorporate new concepts, otherwise they fall into disuse. Those formulating classifications for international application must, however, steer a rather conservative course, as many proposed classification schemes do not stand the test of time. The section on lymphatic and haemopoietic neoplasms of the ICD-O needs revision, and preliminary discussions on appropriate methods have taken place.

[1] Parkin, D. M., Démaret, E. & Crosignani, P. C. (1983) The use of the computer in the cancer registry. *Meth. Inf. Med.*, **22**, 151–155.

(i) *Tenth Revision of the International Classification of Diseases* (Dr C. S. Muir and Mrs J. Nectoux)

A meeting was convened by the WHO Regional Office for Europe in collaboration with the WHO French Centre for Classification of Diseases of INSERM, Le Vesinet, France (23–26 November, 1982) to identify the major problems in the use of the 9th Revision of the International Classification of Diseases (ICD-9) and to formulate proposals for the principles to govern the 10th Revision.

The IARC representative at the meeting raised several problems related to cancer. A recommendation was made that the working formulation on the classification of non-Hodgkin's lymphomas[2] be taken into account in the next revision. It was also pointed out that the comparability in time and space of statistics for cancer and carcinoma *in situ* of the cervix uteri was likely to be compromised if a new terminology[3], Cervical Intraepithelial Neoplasia (CIN), which combines severe dysplasia with carcinoma *in situ* into one category, gained widespread acceptance. This would be particularly unfortunate for the evaluation of cervical cancer screening programmes. A solution meeting the needs of both users has been proposed[4].

(ii) *Multiple tumours* (Dr C. S. Muir)

Multiple malignant primary tumours may occur in an individual at the same or at different times. They may occur at the same or different sites, and any of the foregoing combinations may be of the same or different histological type. There is, however, no clear and general agreement on which grounds these cancers, the frequency of which is growing, should be denoted either as single neoplasms or separate primaries. Part of the current confusion results from a desire to deal with separate facets of the question by the application of one set of rules to cover all situations whether these pertain to calculation of incidence or survival, clinical patient care or etiological research.

The report of a working party (IARC Internal Technical Report No. 83/002) comprising Dr F. Levi (Vaud Cancer Registry, Switzerland), Dr P. Schaffer (Cancer Registry of Bas-Rhin, France), Dr P. Prior (Birmingham and West Midlands Regional Cancer Registry, UK) and Dr C. R. Key (Cancer Registry of New Mexico, Albuquerque, NM, USA), which examined existing schemes for handling multiple primaries and methods of presenting such data was circulated to members of the International Association of Cancer Registries with a series of proposed coding rules devised by Dr J. Staszewski, lately of Gliwice Cancer Registry, Poland. Replies have been received from 38 registries, many of which incorporate detailed comments. When the replies have been analysed, a set of rules will be proposed for such neoplasms.

(*d*) *The mapping of cancer* (Dr C. S. Muir and Mr M. Smans)

(i) *Mortality atlas*

Following publication of *IARC Internal Technical Report* 82/002, which recommended that the Agency embark on the production of a series of international mortality and incidence atlases, visits were paid to national vital statistics offices in Europe by Mr M. Smans and Dr P. Boyle (West

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[2] *The Non-Hodgkin's Lymphomas Pathologic Classification Project* (1982) *Cancer*, **49**, 2112–2135.

[3] Buckley, C. H., Butler, E. B. & Fox, H. (1982) *J. clin. Pathol.*, **35**, 1–13.

[4] Alderson, M., Correa, P., Ford, J., Jensen, O. M., Kupka, K., Miller, A. B., Muir, C. S., Nectoux, J., Waterhouse, J. A. H. & Young, J. L. (1983) *Lancet*, **i**, 1166.

of Scotland Cancer Intelligence Unit, Glasgow, UK) to assess feasibility. Response was very favourable and collaboration promised. Agreement was reached concerning the time period and the size of the administrative divisions to be covered. An outline has been made of the supporting text that would accompany the maps. Data have now been received from the Republic of Ireland, Luxembourg and The Netherlands. The following areas will also contribute: Belgium, Denmark, England and Wales, Federal Republic of Germany, France, Italy, Northern Ireland and Scotland.

Programmes have been written to permit computer drawing of the maps. Work continues on determining the optimum method of presenting the data; there are three possibilities: (a) a series of shades of the same colour, with increasing intensity representing increasing mortality; (b) transition from dark-green for very low rates to dark-red for a very high rates; and (c), as (b), but with use of a third colour to depict the national average.

(ii) *Cancer incidence atlases*

Scotland: Preparation continues of a Scottish cancer incidence atlas. The directors of the Scottish Regional Cancer Registries have agreed to contribute their data, and the work is being coordinated by Dr I. Kemp of the Scottish Information Services Division, Edinburgh. The problems posed by changes in administrative boundaries have been solved and a descriptive text for the country prepared. The boundaries have now been digitized and the general format of the maps decided (see Fig. 12).

German Democratic Republic: The Cancer Registry of the German Democratic Republic (Professor S. Tanneberger, Akademie der Wissenschaften der DDR, Berlin-Buch; and Dr W. H. Mehnert, Nationales Krebsregister, Academy of Sciences of the GDR, Berlin-Johannisthal) may participate in the collaborative production of a cancer incidence atlas for that country.

Nordic Countries: The Nordic cancer registries propose to produce an incidence atlas. The mapping programmes developed at the Agency have been made available to the coordinator for the proposed atlas, Dr O. M. Jensen of the Danish Cancer Registry. Mr Gert Schou visited Lyon to digitize the map for the Nordic countries on the Agency equipment.

State of New York: Dr W. Burnett (State of New York, Department of Health, Albany, NY, USA) has expressed interest in the joint production of an atlas for that state.

(*e*) *Monographs in descriptive epidemiology*

The aim of this segment of the Descriptive Epidemiology programme is to publish data that are considered to be of value in the generation of hypotheses and that are either widely disseminated throughout the literature or not readily available.

(i) *Cancer incidence in migrants to Israel* (Dr D. M. Parkin; in collaboration with Dr R. Steinitz and Dr L. Katz, Israel Cancer Registry, Israel Center for Registration of Cancer and Allied Diseases, Jerusalem; and Dr J. Young, National Cancer Institute, Bethesda, MD, USA)

The Israel cancer registry has collected information on place of birth of all cases registered since 1960, and annual population estimates are available from the Bureau of Statistics. It is thus possible to calculate incidence rates of different cancers in migrants to Israel from several countries or regions. With the accumulation of 16–20 years' data, reliable rates are available even for small migrant groups. It is intended to publish these data in the form of a monograph, comparing

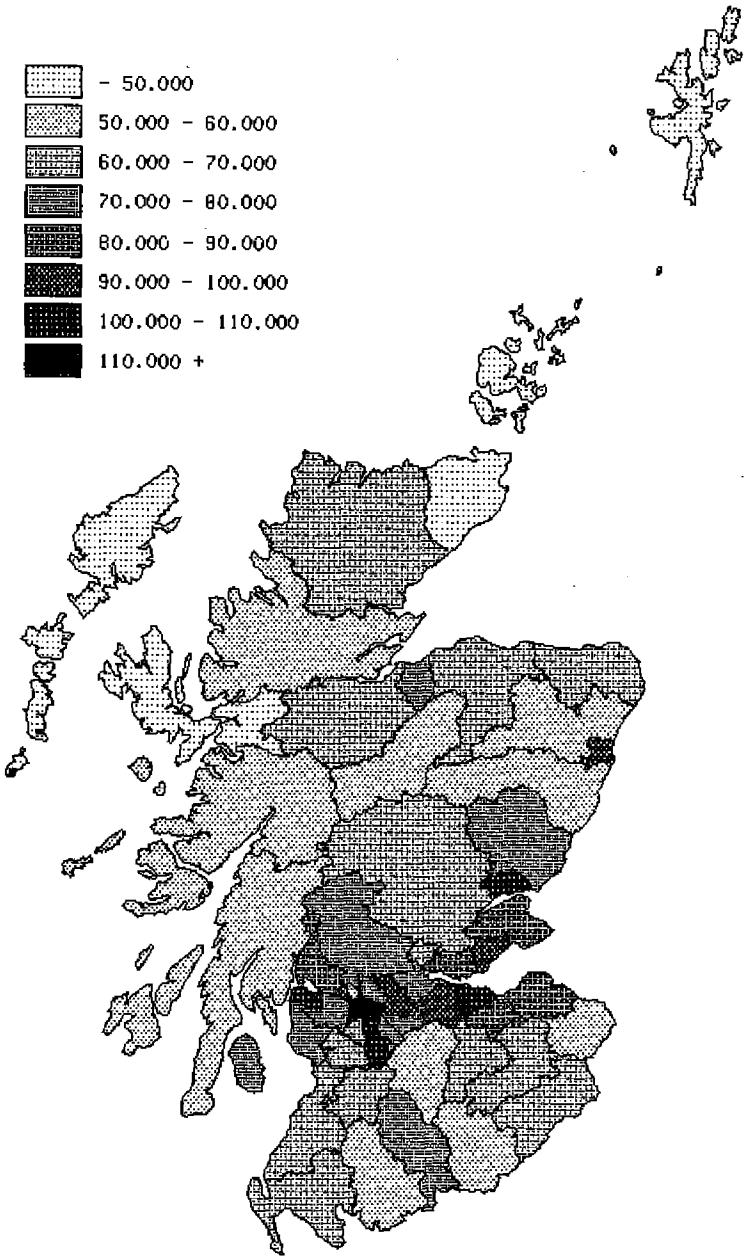


Fig. 12. General format of maps for a cancer incidence atlas of Scotland.

incidence rates between different migrant groups and between migrants to Israel and rates in the country of origin, and studying the rates in relation to period of residence in Israel. Preliminary studies have already been carried out to assess which analyses will be possible.

(ii) *Cancer incidence in Singapore* (Dr N. Day and Mrs A. Arslan; in collaboration with Professor K. Shanmugaratnam and Dr H. P. Lee, Singapore Cancer Registry, Singapore)

A monograph on cancer incidence in Singapore has been published[5]. Evaluation of cancer incidence trends is continuing, and data from 15 years' registration will soon be available.

## 2. DEVELOPMENT OF STATISTICAL METHODOLOGY

### (a) *Development of statistical methods for cancer research*

(i) *Statistical methods for epidemiological studies* (Dr N. E. Day, Dr J. Wahrendorf and Miss M. Blettner; in collaboration with Professor N. E. Breslow, University of Washington, Seattle, WA, USA; Dr C. C. Brown, National Cancer Institute, Bethesda, MD, USA; Mr P. Smith, London School of Hygiene and Tropical Medicine, London)

Work on the effect of matching on the efficiency of testing either for main effects or for interaction has been completed, and a manuscript is now in press[6]. Attention has been turned to the effects of measurement error on estimates of dose-response relationships and on interaction. Means of expressing interaction effects as parameters are under investigation.

Methodological research on assessing the joint effect of several exposures has continued. Emphasis is placed on approaches that illustrate the stochastic variation of data in respect to one or several assumed models simultaneously. This can be achieved by utilizing the 'bootstrap' method, a newly introduced statistical technique which appears to have a broad applicability in epidemiology.

Since many variables in epidemiological research are of the ordinal type—for example, severity of disease, pathological grading and others—methods that have been developed specifically for such data are being reviewed and adapted for use in the epidemiological context.

(ii) *Statistical methods for carcinogenicity studies* (Dr J. Wahrendorf)

Following the finding by specific statistical methods[7] of a negative association between the occurrence of liver tumours and lymphomas and treatment with DDT in CF-1 mice, research has continued on the application of these methods to other data sets of similar nature and on expanding the methods in the light of practical aspects. The data from the so-called '$ED_{01}$' study, comprising 24 192 mice treated with 2-acetylaminofluorene, are being considered for this purpose.

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[5] Shanmugaratnam, K., Lee, H. P. & Day, N. E. (1982) *Cancer Incidence in Singapore, 1968–1977 (IARC Scientific Publications No. 47)*, Lyon, International Agency for Research on Cancer.

[6] Smith, P. G. & Day, N. E. (1983) (submitted for publication).

[7] Wahrendorf, J. (1983) *J. natl Cancer Inst.*, **70**, 915–921.

(iii) *Statistical aspects of mutagenicity experiments* (Dr J. Wahrendorf and Dr G. A. T. Mahon; in collaboration with Dr M. Schumacher, University of Heidelberg, FRG)

A method has been developed for assessing the significance of results from the ames test[8]. The method, based on order statistics, requires simply that a table be consulted to establish the significance of the largest average colony count for the dosed plates, relative to the average counts for the controls. The method is intended especially as an aid to the interpretation of borderline research results.

Work on non-parametric methods has also continued. A critical assessment of the potential of such methods for the analysis of mutagenicity experiments indicates that they are simple, sufficiently robust, and easily applicable for the purpose of significance testing. For descriptive purposes it is essential to include some assumptions of parametric nature, which, however, can be kept to a minimum. These results have led to discussions about standardized designs for mutagenicity experiments.

(*b*) *Dissemination of statistical methods for cancer research*

(i) *The analysis of cohort studies*

The preparation of this publication, a companion volume to the monograph on case-control studies[9], has benefited from the presence of Professor N. E. Breslow at the German Cancer Research Center on a Humboldt Award. Progress during the year has been substantial, The following contents of this monograph are planned:

Chapter 1. Introduction—discussion of the role of cohort studies
Chapter 2. Standardization of rates and proportions
Chapter 3. Elementary approaches to dose-response analysis
Chapter 4. Analysis of cohort results using grouped data
Chapter 5. Analysis of cohort results using individual continous time and exposure variables
Chapter 6. Modelling different dose-time relationships—interpretation in terms of multi-stage models
Chapter 7. Implications for design

Initial drafts of most chapters have been prepared. The sets of data to be used as continuing examples throughout the text have been selected.

(ii) *Statistical analysis of long-term animal experiments* (Dr J. Wahrendorf; in collaboration with Dr J. J. Gart and Dr R. E. Tarone, National Cancer Institute, Bethesda, MD, USA; Dr D. Krewski, Health and Welfare, Ottawa; Mr P. N. Lee, London)

Long-term animal experiments play an important role in identifying cancer risks. Many methodological improvements such as improved design and conduct of the experiments, control of genetic variability, standardization of pathological evaluation, and improvements in statistical methods for analysis, have contributed to this recognition. In the preparation of Supplement 2 of

[8] Mahon, G. A. T. (1983) (submitted for publication).
[9] Breslow, N. E. & Day, N. E. (1980) *Statistical Methods in Cancer Research*, Vol. 1, *The Analysis of Case-Control Studies (IARC Scientific Publications No. 32)*, Lyon.

the *IARC Monographs* series[10], in which 'Basic requirements for long-term assays for carcinogenicity' were outlined and 'Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments' were given, it became apparent that a comprehensive review of all statistical aspects in this field would be timely and would fit very well into the developing series of IARC publications, *Statistical Methods in Cancer Research.*

A working group met in February 1981[11] to outline this project. Work continued through 1982, and in June 1983 another meeting was called to review progress. By that time about three-quarters of the manuscript was available, and it was hoped that the final manuscript would be ready in 1984. This monograph will deal with: (1) general considerations on statistical aspects of long-term animal experiments; (2) qualitative and quantitative aspects of experimental design; (3) standard methods for the analysis of tumour incidence; (4) fitting of statistical models; (5) various special topics, such as multiple statistical comparisons, multiplicity of tumours, litter effects, associations among tumour types, the use of historical controls, and multigeneration experiments; (6) use of concomitant information on survival and body weight; and (7) integration of statistical analyses into the interpretation and evaluation of long-term animal experiments.

(*c*) *Quantitative cancer risk estimation* (Dr J. Wahrendorf, Dr N. E. Day, Dr G. A. T. Mahon, Dr H. Yamasaki and Dr J. R. P. Cabral; in collaboration with Dr J. Kaldor, University of California, Berkeley, CA, USA; supported by the European Economic Community)

A systematic review of published epidemiological studies is being undertaken for those chemicals for which, in Supplement 4 to the *IARC Monographs* series[12], the evidence was characterized as sufficient for them to be classified as carcinogenic to humans, in order to assess the data available for quantitative estimates of risk. For most of these chemicals, accurate information on dose levels of exposure is lacking; information is often available, however, on the time variables related to exposure. Attention will be paid to duration of exposure, time since first exposure, time since last exposure and age as determinants of excess risk. Initial reviews of these data have been prepared for publication[13, 14] and attempts made at interpretation in terms of mode of action within a multi-stage process.

In May, The IARC was host to a first meeting of the Working Group on Time Relationships in Occupational Epidemiology (under the co-chairmanship of Dr J. Goldsmith and Dr D. C. Thomas). An outline was prepared of a monograph which the Group hopes to prepare with a view to publication in the *IARC Scientific Publications* series.

As an experimental component of quantitative cancer risk extimation, large-scale experiments on initiation-promotion on the mouse skin are under way (see p. 86). The statistical analysis of the results of these experiments will be done in close relation to the analysis of epidemiological

[10] IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Suppl. 2, *Long-term and Short-term Screening Assays for Carcinogens: a Critical Appraisal,* Lyon.

[11] International Agency for Research on Cancer (1981) *Annual Report 1981,* p. 55.

[12] IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Suppl. 4, *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29),* Lyon.

[13] Day, N. E. (1983) *Cancer Surv.* (in press).

[14] Day, N. E. & Breslow, N. E. (1983) In: Börzsönyi, M., Day, N. E., Lapis, K. & Yamasaki, H., eds, *Models, Mechanisms and Etiology of Tumour Promotion (IARC Scientific Publications No. 56),* Lyon, International Agency for Research on Cancer (in press).

results. Models that allow incorporation of the different patterns of fractionated promoter application and make reference to the multi-stage theory of carcinogenesis will be considered for this purpose.

(*d*) *Evaluation of early detection programmes*

(i) *Estimation of sensitivity and natural history parameters in cancer of the cervix* (Dr N. E. Day, Dr D. M. Parkin and Mrs A. Arslan; in collaboration with Professor N. W. Choi, Manitoba Cancer Treatment and Research Foundation, Canada; Dr E. A. Clarke, Ontario Cancer Treatment and Research Foundation, Toronto, Canada; Dr J. D. F. Habbema, Department of Public Health and Social Medicine, Erasmus University, Rotterdam, The Netherlands; Dr M. Hakama, The Finnish Cancer Registry, Helsinki; Dr J. E. Macgregor, Department of Pathology, University of Aberdeen, Scotland, UK; Dr K. Magnus, Norwegian Cancer Registry, Oslo; Dr B. Malker, Swedish Cancer Registry, The National Board of Health and Welfare, Stockholm; Dr O. Møller-Jensen, Danish Cancer Registy, Copenhagen, DEB/81/017; Dr F. Pettersson, Department of Pathology, Radium-hemmet, Stockholm; Dr P. Poll, Pathology Department, Central Hospital, Nykøbing F., Denmark; Dr P. Prorok, Biometry Branch, National Cancer Institute, Bethesda, MD, USA; Mr L. Raymond, Geneva Tumour Registry, Switzerland; Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik; DEB/81/018)

With the support of the Danish Cancer Registry and the European Office of WHO, a meeting is planned for October 1983 during which the final results of this collaborative programme will be presented for evaluation. In addition to the centres that were already participating, the Geneva Tumour Registry has been elaborating the results of a case-control study of all cases of cervical cancer registered between 1971 and 1976.

A chapter on the prevention of cervical cancer has been prepared for a WHO monograph on cancer prevention strategies.

(ii) *Breast cancer* (in collaboration with Dr B. J. A. Collette, Preventicon, Utrecht, The Netherlands; and Dr A. Verbeek, Nijmegen University, The Netherlands)

The effects of early detection of breast cancer using mammography, either alone or together with a physical examination, have been under study since the mid 1970s in The Netherlands and Sweden. An invitation was received to participate in a bilateral meeting at Uto, Sweden, in August 1982.

Close contact has developed with the two groups in The Netherlands; a case-control study has been planned in Utrecht to assess the effect on breast cancer mortality.

(iii) *Computer simulation model of cervical cytology screening* (Dr D. M. Parkin and Dr N. E. Day)

Many of the variables pertaining to screening programmes are amenable to alteration: for example, the groups to be examined (defined by age, marital status, parity, etc.), the frequency of screening and the methodology of the test procedure. Simulation models have proved to be a simple means of examining the possible outcome of different screening policies, which would be logistically impossible to evaluate by prospective trials. However, the simulation models used to date suffer from two disadvantages:

(1) They are not easy to validate against real data since they simulate events in single cohorts of women. A stochastic simulation model has been developed which can simulate demographic events in a population resembling that of England and Wales. The impacts of different screening policies that have been recommended can be studied.

(2) They can simulate only very simplistic screening policies. In reality, screening programmes are complex and do not involve examination of women at fixed ages. Much screening is carried out incidentally to other health care contacts (during pregnancy, during gynaecological examinations, in family planning), and individual factors other than age (e.g., previous attendance, marital status) may be used as selective factors for different frequencies of call or recall.

The main defect remains lack of knowledge about the precise natural history of preclinical cervical cancer, and studies to date have cast only limited light. Data that are becoming available from studies in the Nordic countries and Scotland, coordinated by IARC, will help to define the natural history of cervical cancer more precisely.

(*e*) *Development of statistical data bases in cancer epidemiology*

(i) *International study to evaluate risks of radiation exposure in cervical cancer patients* (Dr R. Saracci, Dr G. Engholm, Dr N. E. Day, Dr J. Estève, Miss M. Blettner and Miss D. Magnin; in collaboration with Dr P. Fraser and Dr M. Coleman, London School of Hygiene and Tropical Medicine, London, DEB/81/027; Dr O. Møller Jensen and Dr H. Storm, Danish Cancer Registry, Copenhagen, DEB/81/018; Dr M. Hakama and Dr R. A. Rimpelä, Finnish Cancer Registry, Helsinki, DEB/81/029; Dr K. E. Kjørstad, Norwegian Radium Hospital and Norwegian Cancer Society, Oslo, DEB/81/030, DEB/83/004; Dr F. Pettersson, Karolinska Hospital, Stockholm, DEB/81/031; Dr V. Pompe-Kirn, Slovenian Cancer Registry, Institute of Oncology, Ljubljana, Yugoslavia, DEB/81/036; Dr A. B. Miller, National Cancer Institute of Canada, Toronto, Canada, DEB/82/003; Dr F. Berrino, National Institute for the Study and Therapy of Tumours, Milan, Italy, DEB/82/004; Dr R. Frischkorn, University Women's Clinic, Göttingen, FRG, DEB/82/005; Dr Z. Hlasivec and Dr V. Kubec, Institute of Radiotherapy, Oncological Centre, Prague, DEB/82/007; Professor V. Fournier, University Women's Clinic, Heidelberg, FRG, DEB/82/008; Professor A. Lochmuller, University Women's Clinic, Munich, FRG, DEB/82/009; Dr A. Clarke, Ontario Cancer Treatment and Research Foundation, Toronto, Canada, DEB/82/011; Dr H. Kucera, Clinic of Gynaecology, University of Vienna, DEB/82/012; Dr N. W. Choi, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada, DEB/82/013; Dr K. Sigurdsson and Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik, DEB/83/003; Dr J. D. Boice, National Cancer Institute, Bethesda, MD, USA; Mr P. Smith, London School of Hygiene and Tropical Medicine. Supported by contract NO1-CP-11017 with the US National Cancer Institute)

Previous annual reports have described this study, the purpose of which is to learn about risks associated with exposure to ionizing radiation. The study is an extension of an international study of radiation and leukaemia in cervical cancer patients carried out in 1969–1970 in a large number of clinics in Europe and the US under the sponsorship of the WHO. Most of the clinics which took part in the original study are participating in the present study, in addition to a large number of cancer registries in Europe and North America. The study is being carried out along two lines:

(1) *Cohort study in cancer registries*

On the basis of data from 15 cancer registries in Europe, Canada and the US, the incidence of second primary cancers at all sites in cervical cancer patients treated with radiation was compared with the incidence of primary cancers in the general population. The results of the study will be presented in a monograph, a draft of which was discussed at a meeting in Lyon in January 1983, to be published in the second half of 1983.

(2) *Case-control studies in cancer registries and clinics*

In the cohort study, no detailed information about radiotherapy given to patients was available. In order to describe dose-response relationships, case-control studies are being carried out in which radiotherapy given to each patient will be described in detail. Methods for estimating radiation dose to various organs on the basis of detailed information about radiotherapy are being developed by the Dosimetry Committee under Dr M. Stovall at the M. D. Anderson Hospital and Tumor Institute in Houston, Texas, USA.

Cases were selected from cervical cancer patients who had developed a second primary cancer that met certain criteria of site and time, which were decided upon by the working group primarily on the basis of the results of the cohort study. For each case, two controls will be selected (four for leukaemia cases), matched for year of and age at diagnosis of cervical cancer and survival time after cervical cancer. Controls will be selected from patients who have not developed a second primary cancer. Cases and controls are to be selected both from participating cancer registries and from the collaborating clinics.

In the registries study, cases and controls have been selected from those on which the cohort study was based, and, in addition, some registries have been able to enrol new cohorts. The total number of cases to be included is now of the order of 2350. Some of the registries have already completed abstraction of hospital records for selected patients.

In the clinics study, most of the 30 000 patients enrolled in the original leukaemia study are included, with the addition of another 10 000 enrolled by several clinics. This study is being developed in two phases, the first of which is a follow-up of the cohorts and the second of which is abstraction of hospital records for patients selected as cases or controls. Most clinics have now completed the first phase and have started abstraction of hospital records.

(ii) *Carcinogenic effects of cancer chemotherapy* (Dr N. Day; in collaboration with Dr W. H. Mehnert, Cancer Registry of the German Democratic Republic, Berlin; DEB/83/009; and Dr R. Simard and Mr P. Ghadirian, Cancer Institute of Montreal, Quebec, Canada; DEB/83/008)

The induction of leukaemia by some, or a combination, of the agents used for chemotherapy is well known. Interest lies in determining:

(1) whether an increased risk for solid tumours will emerge as a longer term sequela (bladder cancer following cyclophosphamide treatment has already been noted);

(2) whether risk can be related specifically to certain modalities of chemotherapy;

(3) whether quantitative dose-response relationships can be established for humans. In this respect, study of chemotherapeutic agents provides perhaps the best situation for accurate determination of both dose and response.

The acquisition of useful information in these areas demands large studies, preferably conducted in a number of regions with varying use of chemotherapy. The success of the cervical cancer

radiation study suggested that the development of an international collaborative study among cancer registries would be fruitful. The cancer registries involved in the cervical cancer study have, therefore, been approached, and a meeting was held in January 1983. Agreement was reached that a feasibility study be undertaken, concentrating on second malignancies among patients registered with cancer of the ovary or testes, or Hodgkin's disease. Tabulations are being prepared of observed and expected second malignancies, by site of the second malignancy, interval between the two malignancies, age and time period of diagnosis of the initial cancer, and by broad treatment category. In addition to the cancer registries contributing to the radiation study, contact has been made with the Cancer Registry of the German Democratic Republic, the Cancer Registry of Quebec, Canada, the Cancer Registry of Southern California, USA, and further cancer registries in the United Kingdom.

If these feasibility studies indicate that cancer registry material is sensitive enough to indicate excess risk related to chemotherapy, then it is hoped that case-control studies will be developed in which detailed information on chemotherapy will be sought.

(*f*) *Small-sample properties of some estimators of a common hazard ratio* (Dr A. Walker)

The asymptotic, simulated small-sample behaviour of several estimators of a common hazard ratio are being compared. On a logarithmic scale, a variant of the Mantel-Haenszel[15] estimator first proposed by Rothman and Boice[16] has the least bias among the non-recursive estimators. An inverse-variance weighted average has the smallest variance. The standardized mortality ratio is not preferable on either measure; a two-step estimator[17] appears, on the whole, to be less biased, and to have smaller variance than any of the non-recursive estimators. The maximum likelihood estimator has only marginal further advantages. When small cells dominate the estimates, the log distribution of the latter can be skewed in either direction and be polymodal.

## 3. METHODS FOR DETECTING CARCINOGENS

(*a*) *Evaluation of test systems: in-vivo nitrosation and hepatocarcinogenesis* (Professor M. Roberfroid, Ecole de Pharmacie, Université Catholique de Louvain, Brussels; DEC (RA/78/002)

A new short-term in-vivo test for chemical hepatocarcinogenesis has been developed[18] using the following protocol: Male Wistar rats receive a single injection of a nitrosamine (usually *N*-nitrosodiethylamine, 200 mg/kg). Two weeks later they are fed for two weeks on a diet containing 0.03% 2-acetylaminofluorene. After a further week of normal feeding, the rats receive a diet containing 0.05% phenobarbital (or another promoting agent). They are killed at various time intervals (up to five months), and the livers are analysed both morphologically and histochemically for preneoplastic and neoplastic lesions.

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[15] Mantel, W. & Haenzel, W. (1959) *J. natl Cancer Inst.*, 22, 719–748.

[16] Rothman, K. & Boice, J. (1979) *Epidemiologic Analysis with a Programmable Calculator (NIH Publication No. 79–1649)*, Washington DC, US Government Printing Office.

[17] Anderson, J. & Walker, A. (1983) (submitted for publication).

[18] Lans, M., de Gerlache, J., Taper, H. S., Préat, V. & Roberfroid, M. B. (1983) *Carcinogenesis*, 4, 141–144.

The aim of the present research is to apply this model to evaluate the hepatocarcinogenic potency of *N*-nitroso compounds formed by nitrosation *in vivo* using either morpholine or aminopyrine as precursor.

In order to test the applicability of the protocol, preliminary results have already been obtained: Both *N*-nitrosodiethylamine and *N*-nitrosomorpholine initiated the hepatocarcinogenic process, as revealed by the appearance of γ-glutamyltransferase-positive foci and nodules; both treatments gave a dose-dependent increase in the number of preneoplastic lesions (see p. 112). The same experiments will be done in rats fed morpholine plus nitrite.

Since aminopyrine and nitrite readily produce *N*-nitrosodimethylamine, experiments will also be done in rats receiving either low doses of that nitrosamine (10-50 mg/kg) or aminopyrine and nitrite in amounts that give equivalent doses of *N*-nitrosodimethylamine.

(*b*) *Short-term tests for the detection of carcinogens* (supported in part by CEC contract No. ENV-654-F(S.D.))

(i) *Quantitative comparison of carcinogenicity and mutagenicity of eight directly acting agents* (Mr C. Malaveille, Mrs A. Hautefeuille and Dr J. Wahrendorf)

A previous investigation revealed no positive correlation between the mutagenicity of nine alkylating agents in *Salmonella typhimurium* TA100 and TA1535 and their carcinogenicity ($TD_{50}$) in rodents [19] when mutagenicity was expressed as μmol/L concentration of the test compound to produce 500 revertants per plate. Haynes *et al.* [20] have proposed a possibly improved ranking of the chemicals on the basis of mutagenic efficiency expressed as the slope of the line joining the origin with the maximum number of mutants from a plot: number of mutants per $10^8$ treated bacteria *versus* the dose expressed as lethal hits [–ln(surviving fraction)]. Experiments in TA1535 strain were performed to determine the mutagenic efficiency of eight alkylating agents assayed in our previous study [19]. Results indicated that the parameter of Haynes *et al.* correlated better with the carcinogenicity of these compounds than did the previously used parameter (rank correlation coefficient by Spearman $r_s = 0.52$ and $r_s = 0.1$, respectively). Possibly because of the limited number of compounds investigated, the correlation was not found to be statistically significant.

(ii) *Testing of selected chemicals in multiple short-term assays for the detection of carcinogens-mutagens* (Mr C. Malaveille and Dr H. Bartsch; in collaboration with Dr A. Davis, WHO, Geneva, Switzerland; Dr E. Vogel, Laboratory of Radiation Genetics and Chemical Mutagenisis, University of Leiden, The Netherlands; Dr T. Kuroki, Institute of Medical Sciences, University of Tokyo; Dr C. A. van der Heijden, Laboratory for Carcinogenesis and Mutagenesis, National Institute of Public Health, Bilthoven, The Netherlands; Professor N. Loprieno, Genetics Laboratory, Institute of Anthropology and Human Paleontology, University of Pisa, Italy; Dr M. Umeda, Tissue Culture Laboratory, School of Medicine, Yokohama City University, Japan; supported financially by the Parasitic Disesases Programme, WHO)

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[19] Bartsch, H. Terracini, B., Malaveille, C., Tomatis, L., Wahrendorf, J., Brun, G. & Dodet, B. (1983) *Mutat. Res.*, **110**, 181–219.

[20] Haynes, R. H., Eckardt, F., Kunz, B. A. & Göggelman, W. (1982) In: Sugimura, T., Kondo, S. & Takebe, H., eds, *Environmental Mutagens and Carcinogens*, Tokyo, University of Tokyo Press/New York, Alan R. Liss, Inc., pp. 137–146.

In order to evaluate the possible toxic effects of a molluscicide already in use, bis(tri-*n*-butyltin)oxide (TBTO), a multicentre trial has been initiated to investigate its mutagenic/toxic potential.

Studies on the possible mutagenic activity of TBTO in *Salmonella typhimurium* strains in the presence and absence of fortified Aroclor-treated rat liver post-mitochondrial supernatant (S9) were carried out in the Agency laboratory. TBTO was found to be non-mutagenic but toxic in strains TA100, TA98, TA97, TA1535 and TA1538 in plate and pre-incubation assays. When tested in the *Salmonella*/rat hepatocyte assay, TBTO was also found to be non-mutagenic; however, at concentrations ranging from 0.1–3 µg/ml, TBTO was mutagenic in TA100 strain in the presence of a rat liver S9 metabolic activation system, using the fluctuation test. TBTO was not mutagenic in V79 Chinese hamster cells, as reported previously[21].

No genetic effect was found when TBTO was assayed for: the induction of gene mutations in the yeast *Saccharomyces pombe;* mitotic conversions in the yeast *Saccharomyces cerevisiae;* and sister chromatid exchange in a CHO cell line. In the last assay, the presence of chromosomal structural aberrations and reduplicated and polyphoid cells was seen with a concentration of 5 µg/ml.

In a short-term promotion test, TBTO did not inhibit metabolic cooperation between $HGPRT^+$ and $HGPRT^-$ cells in culture.

Subacute feeding studies were carried out with TBTO in rats to establish the appropriate dose for the carcinogenicity assay. Rats were fed dietary levels of 5, 20, 80 and 320 mg/kg body weight for four weeks, and relevant toxicological end-points were evaluated. All of the dose levels tested had toxic effects; the influence of TBTO on haematopoiesis, the immune system and the nature of erythrocyte rosettes in particular requires further investigation. Further sub-acute experiments and a long-term study in rats are in progress.

TBTO did not induce recessive lethal mutations in *Drosophila melanogaster.* Tests for teratogenic effects *in vitro* and *in vivo* are being completed.

(iii) *Detection of carcinogens in the* Salmonella/*rat hepatocyte assay* (Mr C. Malaveille and Mrs G. Brun)

We have reported previously the efficiency of the *Salmonella*/rat hepatocyte assay for detecting the mutagenicity of chemicals that are carcinogenic to the liver and to other organs[22, 23]. To evaluate this assay further for carcinogens that have not been found to be mutagenic in the *Salmonella*/microsome assay, experiments were carried out with diethylstilboestrol, *N*-diethylnitramine and hydralazine (the latter substance being weakly directly mutagenic). Only hydralazine was metabolized by rat hepatocytes into derivatives mutagenic to *S. typhimurium* TA100 strain. Of 12 carcinogens that are non-mutagenic in the *Salmonella*/microsome assay, four were mutagenic in the *Salmonella*/rat hepatocyte assay. The lack of mutagenicity observed with some of the other compounds tested, such as dioxane, urethane and thiourea, may suggest that the amount of mutagenic metabolites released from rat hepatocytes during in-vitro co-incubation with bacteria is too low to permit their detection. In order to investigate this hypothesis, the rat hepatocyte-DNA alkaline elution assay will be explored, which allows an evaluation of DNA damage within hepatocytes after incubation with the test compound.

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[21] International Agency for Research on Cancer (1983) *Annual Report 1982,* p. 93.
[22] Malaveille, C., Brun, G. & Bartsch, H. (1982) *Carcinogenesis,* 4, 449–455.
[23] International Agency for Research on Cancer (1983) *Annual Report 1982,* p. 94.

(c) *Endogenous formation and detection of carcinogens*

(i) *A dose-response study on* N-*nitrosoproline formation in rats* in vivo *and a deduced kinetic model for predicting carcinogenic effects caused by endogenous nitrosation* (Mr H. Ohshima, Dr G. A T. Mahon, Dr J. Wahrendorf and Dr H. Bartsch)

On the basis of results obtained from a dose-response study on the endogenous formation of *N*-nitrosoproline in rats by concurrent administration of nitrite and proline[24, 25], a kinetic model was formulated to predict carcinogenic effects caused by endogenous nitrosation of amino precursors. Tumour induction by endogenous formation of carcinogenic *N*-nitroso compounds was assumed to depend mainly on (1) the rate of endogenous nitrosation of the amino compound and (2) the carcinogenic activity of the *N*-nitrosamine formed *in vivo*. On the basis of data described in the literature on nitrosation kinetics of selected amines[26] and the carcinogenic potency of the resulting nitrosamines[27], the precursor dose (defined as the dose in μmol[3] per kg body weight per day that will give a 50% tumour yield after two years' exposure) could be determined. The required amounts of precursors (amine, nitrite) calculated from this model were compatible with those reported in previously conducted carcinogenicity experiments. The demonstrated usefulness of this kinetic model for quantitative risk estimation in experimental animals may also allow estimation of carcinogenic risk in humans of endogenously formed *N*-nitroso compounds.

(ii) *Nitrosating properties of bis-methylthiodiiron-tetranitrosyl (Roussin's red methyl ester (RR)), a nitroso compound isolated from pickled vegetables consumed in northern China* (Mr H. Ohshima; in collaboration with Dr A. Croisy, Curie Institute, Orsay, France)

Epidemiological studies have suggested that the consumption of pickled vegetables is a risk factor for developing oesophageal cancer in Linxian County in northern China. Recently, the isolation and identification of Roussin's red methyl ester (RR) from crude extracts of this type of vegetable has been reported[28].

In order to investigate its possible mechanisms of action as a DNA-damaging agent, we synthesized the compound and ascertained its identity by mass sepctrometry[29]. This synthetic compound failed to nitrosate secondary amines *in vitro* under anaerobic conditions, despite the presence of four nitroso groups in the molecule; however, in the presence of oxygen, pyrrolidine and morpholine were efficiently nitrosated when the reaction was carried out in organic solvents or in aqueous medium.

Nitrosation of proline by RR in rats *in vivo* was also studied. The amounts of *N*-nitrosoproline (NPRO) excreted in the 24-h urine of rats given proline in water and RR in acetone, with or without potassium thiocyanate, were measured as an index of endogenous nitrosation. Co-administration of proline and RR resulted in a significant increase in the urinary amount of NPRO compared with those in rats given either proline or RR alone. Administration of thiocyanate together with these

[24] Ohshima, H., Pignatelli, B. and Bartsch, H. (1981) In: Magee, P. N., ed., *Nitrosamines and Human Cancer (Banbury Report 12)*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 297–317.
[25] Ohshima, H., Mahon, G. A. T., Wahrendorf, J. & Bartsch, H. (1983) *Cancer Res.* (in press).
[26] Mirvish, S. S. (1975) *Toxicol. appl. Pharmacol.*, **31**, 325–351.
[27] Druckrey, H., Preussmann, R., Ivankovic, S. & Schmähl, D. (1967) *Z. Krebsforsch.*, **69**, 103–201.
[28] Zhang, W. H., Xu, M. S., Wang, G. H. & Wang, M. Y. (1983) *Cancer Res.*, **43**, 339–341.
[29] Lu, S. H., Camus, A. M., Tomatis, L. & Bartsch, H. (1981) *J. natl Cancer Inst.*, **66**, 33–36.

compounds, however, did not increase the urinary NPRO, although thiocyanate was shown to be an effective catalyst for nitrosation of proline *in vivo* by nitrite or *N*-nitrosodiphenylamine[30].

The nitrosating capacity of RR was compared with that of nitrite. The yield of NPRO after nitrosation by RR *in vivo* was about 220 times less than that of rats given sodium nitrite and proline under the same conditions.

During the course of this study, RR was found to be easily oxidized in the presence of oxygen or air. When this oxidized RR was given to rats together with proline, the amount of NPRO excreted was about two times greater than that found after administration of nitrite and proline.

These results indicate that RR is a weak nitrosating agent, while its oxidized product(s) exhibit a strong nitrosating activity. As the oxidized form of RR may easily be formed or be present in pickled vegetables, further studies are needed to identify and characterize these oxidation product(s).

(iii) *Identification of new* N-*nitroso compounds in human urine* (Mr H. Ohshima, Dr M. Friesen and Dr I. K. O'Neill; in collaboration with Dr D. Fraisse and Dr Q. T. Pham, National Centre for Scientific Research, Vernaison, France)

During the analysis of *N*-nitrosoproline and *N*-nitrososarcosine in urine samples from (undosed) human subjects by gas chromatography, several unknown peaks (Fig. 13, peaks No. 3-5) were detected frequently by the Thermal Energy Analyzer (TEA). The compounds were seen on the chromatogram only when the urine extracts were derivatized with diazomethane and disappeared after treatment with either ultra-violet irradiation at 365 nm or hydrogen bromide/acetic acid; these data suggest that the unknowns may be non-volatile *N*-nitroso compounds.

One of the unknown compounds (peak No. 5), a major unknown which has been detected in almost all the human urine samples analysed to date, was identified as *N*-nitrosothiazolidine 4-carboxylic acid (NTCA) on the basis of identical chromatographic and mass spectral data for the isolated unknown and synthesized authentic compound. The two other unknown *N*-nitroso compounds (peaks nos 3 and 4) have been identified as the 2,4-*trans*- and 2,4-*cis*-epimeric isomers of *N*-nitroso-2-methylthiazolidine 4-carboxylic acid (NMTCA).

These *N*-nitrosamino acids have been detected in many human urine samples, collected in the Poeple's Republic of China, Finland, France and Italy; individual levels are reported elsewhere (see p. 54 and 57). Although their origin in human urine is unknown, intake of a diet supplemented with ascorbic acid appeared to reduce their excretion in the urine (see p. 54). As ascorbic acid is an efficient inhibitor of nitrosation, these data suggest that some NTCA and NMTCA may be formed endogenously. Thiazolidine 4-carboxylic acid and its 2-methyl derivative, the precursor amino compounds of NTCA and NMTCA, are reported to be readily formed by reaction of cysteine with formaldehyde or acetaldehyde, respectively. Thus, measurement of these *N*-nitrosamino acids in urine samples may make it possible to monitor exposure of human subjects to precursors like aldehyde(s) and nitrate/nitrite[31, 32].

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[30] Ohshima, H., Béréziat, J. C. & Bartsch, H. (1982) In: Bartsch, H., O'Neill, I. K., Castegnaro, M. & Okada, M., eds, N-*Nitroso Compounds: Occurrence and Biological Effects (IARC Scientific Publications No. 41)*, Lyon, International Agency for Research on Cancer, pp. 397–411.

[31] Ohshima, H., Friesen, M., O'Neill, I. & Bartsch, H. (1983) *Cancer Lett.*, **20**, 183–190.

[32] Ohshima, H., O'Neill, I. K., Friesen, M., Pignatelli, B. & Bartsch, H. (1983) In: N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)* (in press).

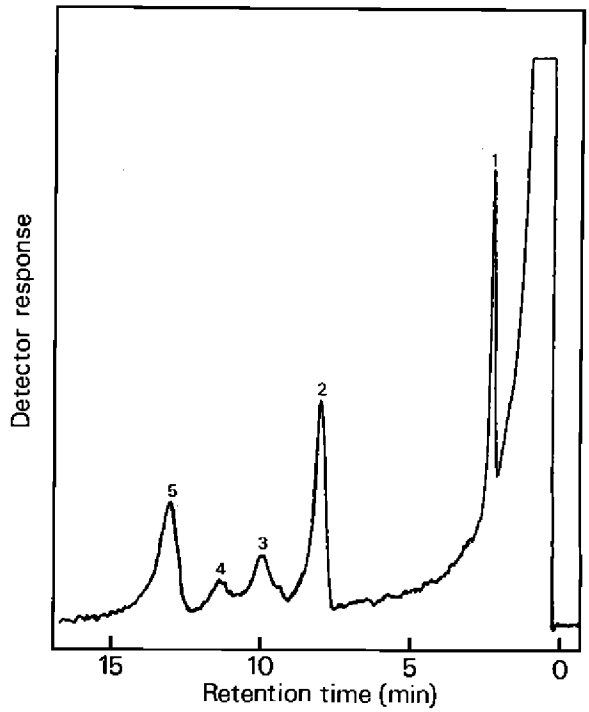


Fig. 13. Identification of new *N*-nitroso compounds in human urine.

(iv) *Excretion of* N-*nitrosamino acids in germ-free and conventional animals* (Mr H. Ohshima; in collaboration with Professor B. Gustafsson, Department of Germfree Research, Karolinska Institute, Stockholm)

As a follow-up of previous studies in conventional rats[33], experiments are being conducted in parallel in both germ-free and conventional rats to examine: (a) the urinary and fecal excretion of administered *N*-nitrosamino acids, (b) their formation *in vivo* from nitrite/nitrate and amino acids and (c) the effects of thiocyanate and ascorbic acid on the formation of *N*-nitrosamino acids *in vivo*. The results are expected to elucidate the role of the gut flora in the formation and the metabolism of *N*-nitrosamino acids.

(v) *Markers to assess individual dietary nitrate intake in human subjects* (Mrs B. Pignatelli, Mr H. Ohshima and Dr H. Bartsch; in collaboration with Professor H. Leclerc and Dr P. Vincent, INSERM, Villeneuve d'Ascq, France)

Two studies are being conducted at INSERM: (1) In 30 human volunteers who have ingested a standard meal rich in nitrate (at a predetermined concentration), the levels of nitrate/nitrite in saliva, blood and urine as well as the pH and the bacteriological state of the saliva are measured; (2)

[33] Ohshima, H., Béréziat, J.-C. & Bartsch, H. (1982) *Carcinogenesis*, **3**, 115–120.

the same subjects who have consumed the nitrate-rich standard meal will also ingest two doses of 250 mg proline one and two hours later. In-vivo nitrosation will be estimated by measuring the levels of *N*-nitrosoproline and other *N*-nitrosamino acids in the urine of each subject in the two series of experiments. An intercomparison of all measured parameters will be made, the final goal being to select for future epidemiological studies those which most reliably assess individual nitrate intake.

(vi) *Influence of catalysts/inhibitors on the formation of* N-*nitroso compounds* in vivo/in vitro (Mrs B. Pignatelli, Mr J.-C. Béréziat and Dr H. Bartsch; in collaboration with Professor G. Descotes, Claude Bernard University and College of Industrial Chemistry, Lyon, France; and Professor R. Scriban, National College of Agricultural and Food Industries, Douai, France; partly supported by the Délégation Générale à la Recherche Scientifique et Technique (DGRST), France)

Polyphenolic compounds (PPC) can enhance or suppress *N*-nitrosation, depending on their structure, the pH and the relative concentration of nitrite *versus* PPC. Recently, catalysis of the nitrosation of proline by resorcinol and catechin and inhibition by chlorogenic acid has been demonstrated both *in vitro* and *in vivo*[34].

Beer contains mixtures of PPC as well as other non-structurally related compounds that could affect *N*-nitrosation. We have therefore studied the role of beer constituents on the formation of *N*-nitroso compounds[35, 36]. Various amounts of lyophilized beer were administered to rats dosed with proline and sodium nitrite and *N*-nitrosoproline excreted in the 24-h urine was monitored as an index of endogenous nitrosation. *In-vitro* formation of *N*-nitrosoproline was determined after 15-min incubation of the same precursor solution. Both *in vivo* (Fig. 14) and *in vitro*, nitrosation of proline was inhibited in a dose-dependent fashion by lyophilized beers of different brands; the effects *in vitro* were most pronounced at pH bellow 4[35].

Some malt and beer samples were treated with polyvinyl pyrrolidone to remove PPC: their inhibitory action on NPRO formation *in vitro* at pH 2.5, although slightly weaker, was not significantly changed[37]. In a comparison of the effect of untreated and treated beer samples on the nitrosation of morpholine *in vitro* at pH 2.5[37], the greatest inhibition was exerted by the untreated beer which contained six times more PPC. Thus, PPC appear to be partly responsible for the inhibitory effect. Several phenolic and cinnamic acids that occur in beer were also tested for their influence on NPRO formation: of the cinnamic acids, ferulic and caffeic acids in particular were more effective than phenolic acids in inhibiting the nitrosation of proline, contributing 10–15% of the inhibition, most of which was due to ferulic acid. Cysteine, which has also been reported to occur in beer, inhibited NPRO formation in a non-linear, concentration-dependent fashion[37].

The inhibitory effects of beer ingredients on *N*-nitrosation may be attributable to PPC, sulfhydryl compounds (e.g., cysteine), other reducing agents and/or other substances. Identification of individual compounds and their relative contributions, is being attempted. As the NPRO method is applicable to human subjects[38], studies to examine the modifying effect of beer constitutents on the nitrosation of proline in man are also under way.

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[34] Pignatelli, B., Béréziat, J.-C., Descotes, G. & Bartsch, H. (1982) *Carcinogenesis*, 3, 1045–1049.
[35] Pignatelli, B., Scriban, R., Descotes, G. & Bartsch, H. (1983) *Carcinogenesis*, 4, 491–494.
[36] Stich, H. F., Dunn, B. P., Pignatelli, B., Ohshima, H. & Bartsch, H. (1983) In: *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)* (in press).
[37] Pignatelli, B., Scriban, R., Descotes, G. & Bartsch, H. (1983) *J. Am. Soc. Brew. Chem.* (in press).
[38] Ohshima, H. & Bartsch, H. (1981) *Cancer Res.*, 41, 3658.

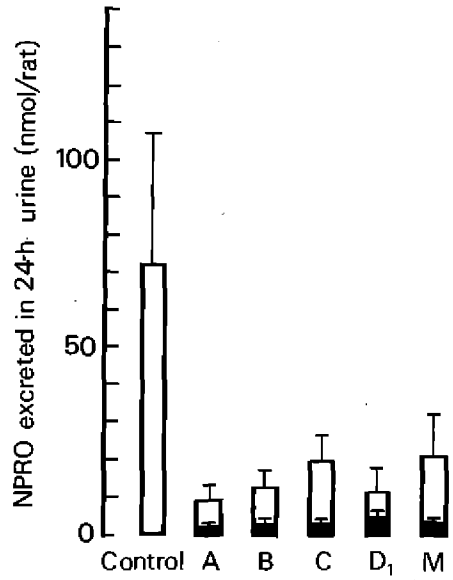


Fig. 14. Effect of lyophilized beers (brands A, B, C, $D_1$) and malt (M) on the formation of *N*-nitrosoproline (NPRO) in rats *in vivo*

(vii) *Development and use of micro-encapsulated trapping agents* (Dr I. K. O'Neill and Mr A. Povey; in collaboration with Professor J. R. Nixon, Chelsea College, University of London)

The aims of this project are to develop methods to quantitate exposure to endogenous carcinogens and their precursors, and to identify hitherto unknown DNA-damaging substances that are formed or are present in the digestive tract of the human body. The approach being followed is to place suitable nucleophilic targets within semi-permeable microcapsules[39], to develop recovery methods, and to utilize highly sensitive detection techniques. The semi-permeable membranes prevent the passage of macromolecules such as degrading enzymes and target macromolecules but permit small molecules such as carcinogens to enter the microcapsules. Microcapsules composed of polyhexamethylenediaminophthalamide, as first developed by Koishi *et al.*[40] are being investigated. Attempts were made to obtain suitable microcapsules with characteristics reproducible from one batch to another, and large-scale preparations have been produced by scaling up a method of Koishi *et al.*, yielding >100 mL of microcapsules of median diameter 8 μ. Magnetic microcapsules, prepared by including suspended haematite in the initial aqueous emulsion, have been prepared in lower yield. However, in both capsule types, mixtures of spherical and non-spherical capsules are produced, thus indicating that further improvement is needed.

Magnetic microcapsules have been successfully passed through the gastrointestinal tract of rats; magnetic recovery has greatly simplified their separation from faeces.

[39] Chang, T. M. S. (1964) *Science*, **146**, 254.
[40] Koishi, M., Fukuhara, N. & Kondo, T. (1969) *Chem. Pharm. Bull.*, **17**, 804–809.

Microcapsules have been prepared, with or without magnetite, containing 5% w/v haemoglobin as a natural trapping agent. When such microcapsules were treated with *N*-[methyl-$^3$H]-*N*-nitrosourea, $^3$H became bound to haemoglobin, although much of the radioactivity was also attached to the membrane. Treatment of microcapsules with aqueous solutions of fluorescein isothiocyanate showed that fluorescence was rapidly fixed throughout the microcapsules, i.e., that molecules of this size (molecular weight, 389) could readily permeate the membrane. Ultrasonication was found to rupture microcapsules. Preliminary work showed that flow cytometry equipment may be useful in characterizing the distribution of size and fluorescence labelling of batches of microcapsules for quality control.

(*d*) *IARC working conference on* N-*nitroso compounds—biological effects and relevance to human cancer* (Dr H. Bartsch, Dr I. K. O'Neill and Dr M. Castegnaro; in collaboration with Dr R. C. von Borstel, University of Alberta, Edmonton, Canada; Dr J. E. Long, Health Protection Branch, Ottawa; and Dr C. T. Miller, Toxic Chemicals Management Centre, Hull, Canada)

The proceedings of the seventh international meeting held in Tokyo were published and contain 73 original presentations and a report on highlights of the meeting[41]. The next conference in the series will be held in Banff, Alberta, Canada from 4–9 September 1983, and the proceedings will also be published in the *IARC Scientific Publications* series. The style of the conference has been altered to include three symposia—on *N*-nitroso compounds in tobacco carcinogenesis, methodological advances in identifying (new) compounds and surveying data linking *N*-nitroso compounds with human carcinogenesis. Approximately 106 proferred papers and 11 invited lectures will be given.

(*e*) *Manuals of selected methods of analysis of environmental carcinogens* (Dr I. K. O'Neill, Dr M. Castegnaro and Dr H. Bartsch; in collaboration with Dr L. Fishbein, National Center for Toxicological Research, Jefferson, AR, USA; and Dr H. Egan, London; supported by UNEP Contract No. FP/1017-79-02(2070))

This series of manuals provides selected methods of analysis for carcinogens (known or suspected) in the environment. Volume 5, *Some Mycotoxins*[42], was published and provides a set of validated methods that were previously unavailable; a compendium of background information was also included. Volume 6, N-*Nitroso Compounds*[43] was also published and provides methods for the wide range of environments in which these substances are found, notably the products of tobacco combustion, endogenous formation and in nutritional and occupational exposures.

The Editorial Board met for the eighth time (Table 17) to consider priorities for future volumes, and a further review was held in February to mark the appointment of Dr L. Fishbein as

[41] Bartsch, H., O'Neill, I., Castegnaro, M. & Okada, M., eds (1982) N-*Nitroso Compounds: Occurrence and Biological Effects (IARC Scientific Publications No. 41)*, Lyon, International Agency for Research on Cancer.

[42] Stoloff, L., Castegnaro, M., Scott, P., O'Neill, I. K. & Bartsch, H., eds (1983) *Environmental Carcinogens - Selected Methods of Analysis*, Vol. 5, *Some Mycotoxins (IARC Scientific Publications No. 44)*, Lyon, International Agency for Research on Cancer.

[43] Preussmann, R., O'Neill, I. K., Eisenbrand, G., Spiegelhalder, B. & Bartsch, H. (1983) *Environmental Carcinogens – Selected Methods of Analysis*, Vol. 6, N-*Nitroso Compounds (IARC Scientific Publications No. 45)*, Lyon, International Agency for Research on Cancer.

Chairman of the Editorial Board in January 1983. Priorities were altered to better reflect availability of analytical information and the numbers of persons believed to be exposed. A further review board on mineral fibres was held in London in June (Table 17).

Table 17. Members of the Eighth Meeting of the Editorial Board and of a Review Board for the Manuals of Selected Methods of Analysis of Environmental Carcinogens

*8th Meeting of the Editorial Board, 28–29 October 1982*

Professor E. Boyland (London School of Hygiene and Tropical Medicine, London)
Professor H. Egan (Laboratory of the Government Chemist, London)
Dr L. Fishbein (National Center for Toxicological Research, Jefferson, AR, USA)
Dr R. Preussmann (German Cancer Research Centre, Institute of Toxicology and Chemotherapy, Heidelberg, FRG)
Dr P. L. Schuller (National Institute of Public Health, Bilthoven, The Netherlands)
Dr R. W. Stephany (National Institute of Public Health, Bilthoven, The Netherlands)
Dr F. Valic (International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland)

*Review Board on Mineral Fibres, 29 June 1983*

Professor E. Boyland (London School of Hygiene and Tropical Medicine, London)
Dr A. Critchlow (Health and Safety Executive, Sheffield, UK)
Dr B. Carton (Institut National de Recherche et de Sécurité, Vandœuvre, France)
Professor H. Egan (Laboratory of the Government Chemist, London)
Dr P. Elmes (South Glamorgan, UK)
Dr T. Ogden (Health and Safety Executive, London)

Volume 7, on certain elements and their compounds, was commenced, and the outline of the volume was presented for comment and feedback at the International Symposium 'Health Effects and Interactions of Essential and Toxic Elements' in Lund, Sweden and at the 'Workshop on Carcinogenic/Mutagenic Metals' in Geneva, Switzerland. Volume 8, on volatile halogenated aliphatic compounds, was also commenced. Consideration was given to preparing a future volume on passive smoking, to include methods for measurement of tobacco sidestream smoke, ambient air concentrations and biological indices of past exposure, and to coordinate the volume with planned evaluations at the Agency of carcinogenic risk of tobacco smoking and passive smoking. Volumes on formaldehyde, benzene, dioxane and biological monitoring methods are anticipated in future years.

The volumes and chief external collaborators foreseen are as follows:

*Certain Elements and their Compounds,* Dr P. L. Schuller, Rijks Instituut voor Volkgesondheid, Bilthoven, The Netherlands

*Halogenated Alkanes and Alkenes,* Dr L. Fishbein, National Center for Toxicological Research, Jefferson, AR, USA

*Passive Smoking,* Dr D. Hoffmann, American Health Foundation, Valhalla, NY, USA

*Mineral Fibres,* Dr A. Critchlow, Health and Safety Executive, Safety in Mines Research Establishment, Sheffield, UK

(*f*) *International network of carcinogenicity testing* (Mr J. Wilbourn, Dr H. Vainio, Dr J. R. P. Cabral and Dr R. Montesano)

In spite of the growing importance of short-term tests, long-term carcinogenicity assays still remain the only ones that can provide conclusive experimental evidence on the carcinogenicity of chemicals. Because of the relatively small number of facilities, the escalating cost of performing long-term bioassays and the large number of chemicals for which carcinogenicity data are lacking or are inadequate, it has become critical to establish criteria for selecting chemicals and complex mixtures for testing and to coordinate such testing.

Over the past several years, the Agency, in collaboration with the International Programme on Chemical Safety (WHO), has therefore established a network of laboratories in which chemicals are tested. The aims of the project are to select chemicals of high priority for study and to coordinate their testing within various collaborating laboratories and, to a limited extent, within the Agency's facilities. The majority of studies involve the long-term testing of chemicals for carcinogenicity in rodents, although some deal with the development and validation of new tests in in-vivo systems. Certain areas of research are useful in evaluating the carcinogenic effects of chemicals and in estimating risks for human health from exposure to environmental carcinogens; these include investigations of combined effects (additive, synergistic or inhibitory) of exposures to low doses of various agents; dose-response studies, especially for extrapolation from high to low doses; investigations of the effects of various treatment schedules, such as fractionated doses and different lengths of exposure; studies of transplacental carcinogenesis; and multigeneration carcinogenicity experiments.

Priorities for testing are reviewed with the help of expert consultants, taking into account the evaluations of chemicals considered in *IARC Monographs,* studies underway or planned in various national toxicology programmes, and priorities established by the International Programme on Chemical Safety (WHO). Reference is also made to the IARC *Information Bulletins on the Survey of Chemicals Being Tested for Carcinogenicity* (see p. 139) to determine if studies are already underway elsewhere. The following factors are also taken into account during the selection of chemicals and complex mixtures:

- environmental occurrence and human exposure;
- segment of population (age, number) at potential risk;
- quantities produced and use patterns;
- stability and persistence in the environment;
- structure-activity relationships with known carcinogens and/or mutagens;
- known mutagenicity or chemical reactivity with DNA, other marcromolecules or nucleophiles;
- possible presence of carcinogenic impurities in compounds previously reported as giving positive results in carcinogenicity tests;
- availability of compounds; whether as technical or purified grade;
- national requirements.

Carcinogenicity testing of chemicals, including the design of protocols, is carried out in accordance with guidelines given in Supplement 2 to the *IARC Monographs*[44] with the aim of improving and standardizing testing procedures. The principal investigators and the studies

[44] International Agency for Research on Cancer (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Suppl. 2, *Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal,* Lyon.

underway or planned in the various collaborating laboratories in the network are given in Table 18. Collaboration with participating laboratories is implemented through ad-hoc research agreements drawn up for limited periods of time covering the specific task to be performed. The selection of laboratories is under continuous review.

Table 18. Principal investigators and studies underway or planned in the international network for carcinogenicity testing

Börzsönyi, M. (National Institute of Public Health, Budapest, DEC/81/035):
- Long-term study on atrazine by oral administration to rats—pre-chronic study completed
- Long-term study in rats on simazine by oral administration to rats—planned

Cabral, R. (International Agency for Research on Cancer, Lyon, France):
- Pre- and post-natal exposure of rats to styrene oxide by oral administration—completed and report in preparation (Preliminary findings of an increased incidence of neoplastic lesions of the forestomach in animals of both sexes have been reported[45])
- Long-term study on deltamethrin by oral administration to mice and rats—in progress
- Long-term study on fenvalerate by oral administration to mice—in progress

Chernozemsky, I. (Institute of Oncology, Sofia, DEC/80/012):
- Long-term study on spironolactone by oral administration to rats—planned

Griciute, L. (Oncological Institute of the Ministry of Health of the Luthuanian SSR, Vilnius, Lithuania, USSR, DEC/81/009):
- Long-term study on benzo[*a*]pyrene, ethylene oxide and styrene, alone or in various combinations, by oral administration to mice—in progress

Kung-Võsamäe, A. (Institute of Experimental and Clinical Medicine of the Ministry of Health of Estonian SSR, Tallin, Estonia, USSR, DEC/81/008):
- Long-term study on Estonian shale oil fly ash by intratracheal administration to rats—in progress

Roberfroid, M. (Unit of Toxicological Biochemistry, Catholic University, Brussels, DEC/82/006):
- Study of diazepam and oxazepam in the rat-liver two-stage model for capacity to induce preneoplastic lesions—in progress

Rossi, L. (Institute of Oncology, University of Genoa, Italy, DEC/80/013):
- Long-term study on chloramphenicol by oral administration to mice—in progress
- Transplacental exposure study on diazepam in mice—in progress
- Long-term study on fenvalerate by oral administration to hamsters—planned

Turusov, V. (Oncological Research Centre, Moscow, DEC/81/034):
- Effects of fractionated doses and varying dosage schedules on carcinogenicity of 1,2-dimethylhydrazine in mice—in progress

van der Heijden, C. A. (National Institute for Public Health, Bilthoven, The Netherlands):
- Long-term study on tributyltinoxide by oral administration to rats—in progress

Long-term animal experiments that relate mainly to the study of specific mechanisms of carcinogenesis are described on p. 75.

[45] Ponomarkov, V., Cabral, J. R. P., Wahrendorf, J. & Galendo, D. (1983) *Toxicologist*, 3, 46.

(g) *Immunological and biochemical technqiues for detecting exposure to carcinogens* (in collaboration with the International Programme of Chemical Safety, WHO, Geneva)

(i) *Development of radioimmunoassays for monitoring exposure to aflatoxin $B_1$* (Dr P. Sizaret, Miss B. Chapot and Dr R. Montesano; supported by the Ministry of Health, Paris)

Previous studies[46, 47] showed that polyclonal antibodies to aflatoxin $B_1$ (coupled to bovine serum albumine at the $C_8$ position) react in radioimmunoassays with various aflatoxin metabolites, including aflatoxin $M_1$. This methodology therefore appears particularly useful for measuring aflatoxin(s) in the urine of people exposed to this carcinogen. During the last year, an enzyme-linked immunosorbent assay was being developed in order to measure the sensitivity of the assay.

(ii) *Detection of DNA alkylated bases in human tissues* (Dr D. Umbenhauer, Miss B. Chapot and Dr R. Montesano; in collaboration with Dr M. Rajewsky, Institute for Cell Biology Tumour Research, University of Essen, FRG; Dr R. Saffhill, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK; and Dr S. H. Lu, Cancer Institute, Chinese Academy of Medical Sciences, Beijing; DEC/81/002)

There is a strong correlation from studies in experimental animals between the formation and persistence of $O^6$-alkylguanine and the susceptibility of certain tissues to carcinogenesis by alkylating chemicals. However, the actual relevance of this base in the etiology of human cancer has not yet been demonstrated. Sensitive radioimmunoassay techniques now permit the analysis of $O^6$-alkylguanine at levels that are relevant to human exposure to alkylating carcinogens.

In collaboration with Dr Lu, human surgical tissue has been obtained from patients in Linxian county, People's Republic of China, an area in which there is an extremely high risk of oesophageal cancer. There is good evidence that the inhabitants of the area are exposed to nitrosamines or nitrosamine precursors, especially those which are likely to form methylating or ethylating agents. DNA has has been isolated from 'uninvolved' oesophagus, stomach and oesophageal tumours. A high-performance liquid chromatographic system for separating $O^6$-alkyldeoxyguanosines from parental nucleosides is being developed so that a series of $O^6$-alkyldeoxyguanosines can be analysed from the same DNA sample. In collaboration with the laboratories in Essen and Manchester, high-affinity monoclonal antibodies against $O^6$-methyl, -ethyl, and -butyl deoxyguanosine are being used in radioimmunological detection of these DNA adducts.

Since it is widely believed that the presence of $O^6$-alkylguanine in DNA at the time of replication is important in the initiation stage of carcinogenesis, the ability of a tissue to repair the lesion can determine in part its sensitivity to carcinogenesis. Protein extracts have been prepared from the surgical specimens and analysed for their ability to remove $O^6$-methylguanine from a DNA substrate in an in-vitro assay. The oesophageal extracts removed $O^6$-methylguanine more efficiently than did the stomach tissue, while the tumour tissue had the greatest capacity of the three. Experiments are now underway to determine the ability of the same extracts to remove $O^6$-ethylguanine from DNA in a similar assay (see also p. 75).

[46] Sizaret, P., Malaveille, C., Montesano, R. & Frayssinet, C. (1982) *J. natl Cancer Inst.*, **69**, 1375–1381.
[47] Sizaret, P. & Malaveille, C. (1983) *J. Immunol. Meth.* (in press).

(iii) *Monoclonal antibodies against* $O^6$*-methylguanine* (Dr R. Saffhill, Dr C. P. Wild and Dr J. M. Boyle, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK; DEC/83/001)

In order to improve the sensitivity of conventional (radiochromatographic) methods for studying the alkylation of cellular DNA, we have developed very sensitive radioimmunoassays (using mouse monoclonal hybridoma cell lines) to detect specific alkyl products in DNA at fmol levels[48, 49]. Using these assays in conjunction with a simple, fast chromatographic separation, we have quantitated $O^6$-methylguanine formation and removal using small DNA samples derived from as few as $10^6$ cells and detected very low levels of alkylation using larger amounts of DNA. Thus, with a DNA sample of 2 mg it is possible to detect about 100 $O^6$-methylguanine residues per cell. These methods should permit detection of environmental exposure to alkylating agents.

## 4. SURVEY OF EXISTING COLLECTIONS OF HUMAN BIOLOGICAL MATERIAL (Dr G. Lenoir, Dr A. Walker and Professor R. Sohier; in collaboration with Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik)

In view of the conclusion of the Agency's Scientific Council in 1982 that epidemiological studies frequently generate the need for development of new laboratory techniques (which sometimes appear too late for incorporation into the analysis of the study which stimulates them), it has been proposed to make an inventory of existing collections of biological materials before envisaging the creation of new banks.

In order to initiate this activity, a circular letter and a questionnaire were sent during the summer of 1982 to 1080 persons whose names and addresses were on file in the Clearing-house for On-Going Research in Cancer Epidemiology (see p. 138). Personal letters were sent to 260 additional persons whose names were provided by scientists working in the area, and staff members responsible for laboratory services in each Regional Office of WHO were also contacted. Furthermore, in October 1982, letters were sent to 30 countries through the official channel of the Ministries of Health. In April 1983, the same material was sent to the deans of all 780 medical schools throughout the world.

By the beginning of July 1983, a total of 570 replies had been received, 230 of which contained positive information on collections. These positive questionnaires were coded and tallied according to: type of material collected, number of individual samples, time since collection, location of banks, target populations, traceability as to location of the sample as well as potential for following up the individuals who had donated material; whether more than one type of material had been collected per individual or whether sequential samples had been collected. In January-February 1983, a computerized file was created on all people who had been written to; this serves as a source of addresses and for the selection of lists according to certain criteria such as geographical location and type of sample.

The analysis will continue along similar lines. Consideration will be given to the feasibility of utilizing the banks for particular, exemplary projects.

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[48] Saffhill, R., Strickland, P. T. & Boyle, J. M. (1982) *Carcinogenesis*, 3, 547–552.
[49] Wild, C. P., Smart, G., Saffhill, R. & Boyle, J. M. (in preparation).

The Agency continues to prepare and to distribute working sera for studies of Epstein-Barr virus. Other sera and biological samples collected within the framework of the Agency's projects are also distributed on request, whenever possible.

The Agency also continued to provide the 78/610 reference preparation for assay of the specific pregnancy glycoprotein, SP1, as well as the 72/225 WHO α-fetoprotein standard. Since April 1983, these standards have been distributed by the Department of Biological Standardization, Statens Seruminstitut, Amager Boulevard 80, 2300 Copenhagen, Denmark.

## 5. DESTRUCTION OF CARCINOGENIC WASTES FROM LABORATORIES (Supported by NCI Contract NOI-DS-2-2130)

Implementation of this programme involves the following five steps:

(1) collection of available data related to degradation techniques and the chemistry of the carcinogens or classes of carcinogens considered;
(2) evaluation of bibliography and preparation of intermediate documents;
(3) evaluation in the laboratory of the efficiency of the proposed methods and, when necessary, elaboration of new methods;
(4) initiation of collaborative studies to ascertain the efficiency of the methods;
(5) critical review of the document, before final publication as an *IARC Scientific Publication*, by a meeting of experts drawn from the group of participants in the collaborative study.

### (a) *Collection of data* (Dr M. Castegnaro)

Updating of the literature on polycyclic aromatic hydrocarbons, nitrosamides, hydrazines, chloroethers and aromatic amines has been performed using available on-line facilities.

### (b) *Evaluation of bibliography and preparation of individual monographs* (Dr M. Castegnaro; in collaboration with Mr E. A. Walker, London)

An intermediate document on the decontamination of wastes contaminated with aromatic amines has been prepared; and documents concerning nitrosamides, hydrazines and chloroethers have been revised and updated.

### (c) *Assays and development of methods*

#### (i) *Chemical degradation of hydrazines and mutagenicity testing of residues* (Dr M. Castegnaro, Mrs I. Brouet, Miss J. Michelon and Mr C. Malaveille; in collaboration with Dr E. B. Sansone, Chief, Environmental Control and Research Programme, NCI-Cancer Research Facility, Frederick, MD, USA; and Dr H. E. Malone, Sanitary Facilities Manager, Special Districts Department, San Bernardino, CA, USA)

Suitable methods for residual analysis of hydrazines after degradation were developed, and four were investigated with five hydrazines: hydrazine, monomethylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine and procarbazine. The four methods were:

(A) reduction with nickel-aluminium alloy under alkaline conditions;
(B) oxidation by potassium iodate under acidic conditions;
(C) oxidation by potassium permanganate under acidic conditions[50]; and
(D) oxidation by hypochlorites (sodium or calcium).

All three oxidation methods were tested both for degradation of hydrazines and possible formation of nitrosamines. Mutagenicity testing has also been performed on the residual solutions after degradation [see section (iii) below].

Samples of each of the hydrazines tested were treated by Methods B, C and D (section (i) above). After checking the efficiency of degradation by Methods C and D, excess ascorbic acid was added to samples to destroy the excess of oxidant. The reaction media were then made alkaline, centrifuged to remove the precipitate and neutralized to pH 7.1. Samples obtained after treatment by Method B were directly neutralized to pH 7.1. These media were then tested for mutagenicity, using the Ames test on *Salmonella typhimurium* strains TA1530, TA1535 and TA100, and additionally with TA98 for degradation products of procarbazine, with and without metabolic activation by a (Aroclor-induced) rat liver microsomal preparation. The results were as follows:

Method B: No mutagenic effect could be deteted in strain TA1530, TA1535 or TA100
Method C: Slight mutagenic activity (twice the background) was detected in strains TA1530 and TA1535, without activation, at levels equivalent to 100 µg/plate of the original compound. No mutagenicity could be detected in TA100 or TA98 with the same levels of the original undegraded compounds.

Table 19. Mutagenicity of residues of degradation of hydrazine and 1,1-dimethylhydrazine by calcium hypochlorite

| Strain | Activation system[a] | Equivalent amount per plate (mg) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hydrazine | | | | | 1,1-Dimethylhydrazine | | | | |
| | | 1.4 | 0.7 | 0.35 | 0.18 | 0.09 | 1.4 | 0.7 | 0.35 | 0.18 | 0.09 |
| TA1530 | + | 101 | 21 | 0 | 0 | 0 | 26 | 66 | 47 | 27 | 22 |
| | − | 867 | 555 | 373 | 152 | 63 | T | T | 397 | 565 | 194 |
| TA1535 | + | 97 | 21 | 8 | 0 | 0 | 96 | 121 | 51 | 35 | 25 |
| | − | 810 | 479 | 535 | 170 | 88 | T | 220 | 841 | 776 | 282 |
| TA100 | + | 26 | 3 | 1 | 0 | 0 | T | 71 | 54 | 65 | 42 |
| | − | 183 | 148 | 74 | 19 | 0 | T | T | T | 161 | 113 |

[a] With (+) or without (−) an Aroclor-induced rat liver 9000 × *g* supernatant metabolic activation system
T, toxic

[50] Castegnaro, M., Eisenbrand, G., Ellen, G., Keefer, L., Sansone, E.B., Spincer, D., Telling, G. & Webb, K., eds (1982) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some N-Nitrosamines (IARC Scientific Publications No. 43)*, Lyon, International Agency for Research on Cancer.

Method D: Very high mutagenicity was found, without metabolic activation, for degradation products of hydrazine and 1,1-dimethylhydrazine (Table 19), and moderate mutagenicity for those of monomethylhydrazine, 1,2-dimethylhydrazine and procarbazine. When the ratio of oxidant to hydrazine was changed by a factor of four and the reaction time increased to about 12 h, no mutagenicity could be detected in degradation media from hydrazine and monomethylhydrazine, and only one to three times the background level on TA1530 and TA1535 for the degradation media of 1,2-dimethylhydrazine and procarbazine. Mutagenic activity of up to 10 times the background level was still detected in the degradation medium of 1,1-dimethylhydrazine.

The mutagenicity of samples of hydrazines treated by method A is being investigated.

(ii) *Chemical degradation of nitrosamides and mutagenicity testing of residues* (Dr M. Castegnaro, Miss J. Michelon and Mr C. Malaveille; in collaboration with Dr E. B. Sansone, NCI-Cancer Research Facility, Frederick, MD, USA)

Four methods have been investigated on five nitrosamides: *N*-nitrosomethylurea, *N*-nitrosoethylurea, *N*-nitrosomethylurethane, *N*-nitrosoethylurethane and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.The methods were:

(A) denitrosation in 3 mol/L hydrochloric acid in the presence of sulfamic acid;
(B) denitrosation in 3 mol/L hydrochloric acid in the presence of iron filings;
(C) denitrosation with a 3% solution of hydrobromic acid in glacial acetic acid; and
(D) oxidation by potassium permanganate under acidic conditions.

Method A: 17 g of any of the nitrosamides tested, solubilized in 1 L 3 mol/L hydrochloric acid are denitrosated in 24 h, and 35 g sulfamic acid are sufficient to trap the nitrogen oxides formed.

Method B: 17 g of any of the nitrosamides tested solubilized in 1 L 3 mol/L hydrochloric acid are denitrosated in 24 h, and 35 g iron are sufficient to cause reduction of the nitrogen oxides formed.

Samples of each of the nitrosamides listed above after treatment with Methods A, B, C and D are being tested for mutagenicity using the Ames test on *Salmonella typhimurium* strains TA1530, TA1535 and TA100.

(iii) *Assay, development of methods and mutagenicity testing of residues of degradation of polycyclic aromatic hydrocarbons* (Dr M. Castegnaro, Mrs I. Brouet, Miss M. C. Bourgarde and Mr C. Malaveille; in collaboration with Dr M. Coombs, Imperial Cancer Research Fund, London)

Extracts from residues of treatment of selected polycyclic aromatic hydrocarbons (PAH) by Method A[51] (saturated solution of potassium permanganate) and Method B[51] (potassium permanganate under acidic conditions) have been tested for mutagenicity, using *Salmonella typhimurium* strain TA100, in Dr Coombs' laboratory; these compared very well with those obtained at the Agency[52]. The data were presented at a conference in Battelle (Columbus, OH, USA)[53].

[51] International Agency for Research on Cancer (1983) *Annual Report 1982*, pp. 108-109.
[52] International Agency for Research on Cancer (1983) *Annual Report 1982*, p. 109.
[53] Castegnaro, M., Coombs, M., Phillipson, M., Bourgade, M. C. & Michelon, J. (1982) In: *Proceedings of the 7th International Symposium on Polynuclear Hydrocarbons, Battelle, Columbus Laboratories, 26–28 October 1982* (in press).

Method C[51] (treatment with 18 mol/L sulfuric acid) has been reinvestigated and the residues extracted into cyclohexane and ethyl acetate were tested for mutagenicity, using *S. typhimurium* strains TA98 and TA100 with and without metabolic activation. Increasing the ratio of sulfuric acid to PAH by a factor of two reduced the mutagenic effect to less than twice the background level for 900 µg equivalent of PAH per plate.

Cyclohexane and ethyl acetate extracts of residues obtained by treatment of some PAH by Method D[54] (50% diluted mixture of chromic acid/sulfuric acid) were also tested in the Ames test, as described above. Only in rare cases was a mutagenic effect below the two-fold background level detected; all other samples were non-mutagenic.

(iv) *Evaluation of decontamination techniques* (Dr M. Castegnaro; in collaboration with Dr P. Chambon, Faculty of Pharmacy, Lyon, France; Mr B. Langlais, 'Trailigaz' General Ozone Company, Garges-les-Gonesses, France; and Dr M. Coombs, Imperial Cancer Research fund, London)

(1) *Ozonization:* The efficiency of ozonization for treating solutions of benz[*a*]anthracene, 7,12-dimethylbenz[*a*]anthracene and 3-methylcholanthrene has been investigated. Under similar conditions to those applied for the degradation of benzo[*a*]pyrene[55], degradation better than 99.9% was achieved. Mutagenicity testing of the residues obtained by this method is in progress.

(2) *Catalytic pyrolysis:* The catalytic pyrolysis unit, which was built at the Agency and which proved efficient for the degradation of aflatoxins, whether in solutions in chloroform, methanol or water, has been transferred to Dr Coombs' laboratory. He has now evaluated its efficiency for the degradation of polycyclic aromatic hydrocarbons.

For the degradation of 10 mg of parent compound solubilized in methanol, the following conditions of degradation were applied to solutions containing 0.5 mg/min, at a solvent flow rate in the furnace of 0.5 mL/min and a catalyst temperature of 500°C. The degradation levels were: benzo[*a*]pyrene (98.6%), chrysene (94%), benz[*a*]anthracene (98.3%), 15,16-dihydro-11-methylcyclopenta[*a*]phenanthrene-17-one (96.8%) and 2-acetylaminofluorene (90%).

Work is in progress to optimize the conditions of operation to achieve better degradation levels.

(v) *Degradation of aromatic amines and mutagenicity testing of residues* (Dr M. Castegnaro; in collaboration with Dr M. Lafontaine, INRS, Vandœuvre, France; and Dr J. Barek, Charles University, Prague)

A method using diazotization has been evaluated at INRS for the treatment of 4,4'-methylene bis(2-chloroaniline). A very efficient chemical degradation was obtained, and the residues from this method were accordingly tested for mutagenicity, both at the Agency and at INRS: strong mutagenic effects were detected, with and without metabolic activation. The method will, therefore, be reconsidered.

The method for the degradation of aromatic amines using oxidation by potassium permanganate under acidic conditions has been successfully evaluated in Dr Barek's laboratory, for benzidine, *o*-tolidine and *o*-anisidine. Work is in progress in that laboratory to evaluate the efficiency of the method for other aromatic amines, and at the Agency to study the mutagenicity of the residues.

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[54] International Agency for Research on Cancer (1983) *Annual Report 1982*, pp. 108–109.
[55] International Agency for Research on Cancer (1983) *Annual Report 1982*, p. 109.

(vi) *Extraction of polycyclic aromatic hydrocarbons from oily solutions* (Dr M. Castegnaro; in collaboration with Dr W. Karcher, Petten Establishment, Joint Research Center, Commission of the European Communities, Petten, The Netherlands)

Upon request of the board revising the document on methods of destroying polycyclic aromatic hydrocarbons, a short method for their extraction from olive oil was devised in Dr Karcher's laboratory and subsequently tested successfully in a collaborative study (see below).

(*d*) *Initiation of collaborative studies* (Dr M. Castegnaro)

Upon request of the board revising the document on degradation methods for polycyclic aromatic hydrocarbons, a small study was initiated to confirm the efficiency of concentrated sulfuric acid, both for the decontamination of glassware and for pure compounds, and to test the extraction method devised in Dr Karcher's laboratory for the extraction of PAH from oily solutions.

Two collaborative studies to test methods for the degradation of hydrazines and nitrosamides have been organized. The first involves six laboratories in France, The Netherlands and the USA; and the second, 11 laboratories in France, FRG, The Netherlands, Italy, the UK and the USA.

(*e*) *Final evaluation of documents and publication*

Upon receipt of the results of the collaborative study organized in Lyon in the spring of 1982 to evaluate methods of degradation of polycyclic aromatic hydrocarbons, a meeting was organized in September 1982 to revise the corresponding document. Three of the four proposed methods were maintained in the document; the fourth—treatment with a 50% diluted mixture of chromic acid/sulfuric acid—although it gave good degradation yields and residues with very low mutagenic effect, was rejected, as legislation in several countries prohibits the disposal of chromate. Results from the complementary study organized in December 1982 (see section (*d*) above) were included in the document, published early in 1983[56].

Meetings to finalize the documents on hydrazines and nitrosamides were held in June 1983.

[56] Castegnaro, M., Grimmer, G., Hutzinger, O., Karcher, W., Kunte, H., Lafontaine, M., Sansone, E. B., Telling, G. & Tucker, S. P., eds (1983) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Polycyclic Aromatic Hydrocarbons (IARC Scientific Publications No. 49)*, Lyon, International Agency for Research on Cancer.

# TECHNICAL SUPPORT

## 1. COMPUTING SERVICES AND STATISTICAL SUPPORT (Dr J. Estève, Mr M. Smans, Dr J. Wahrendorf, Miss B. Charnay, Mr P. Damiecki, Mrs A. Arslan, Mr M. Jaboulin and Mrs B. Kajo)

Besides its activity in the various scientific programmes described in earlier parts of the report, the Unit of Biostatistics has traditionally given consultation in statistics and computing. This activity is increasing, and, with the development and awareness of modern computing techniques, the demand for computing consultation of various types becomes heavier and will probably need special consideration in the future.

The development of ad-hoc software is continuing and two new interactive tools have been added to the existing 'easy-to-use' package for scientists. The first makes available the data from *Cancer Incidence in Five Continents* on line and enables quick consultation of indices of incidence according to site, registry age, etc. The second is a package of bibliographic reference retrieval which enables the management of personal collections of reprints according to various criteria defined by the user.

Statistical consultations for day-to-day problems of experimental research are given increasingly. In many cases, such consultations are the starting point for joint activities such as those reported in preceding parts of this report.

## 2. BIBLIOGRAPHIC SUPPORT

### (*a*) *Library services* (Mrs A. Nagy-Tiborcz and Mrs L. Ossetian)

The Agency subscribes to 230 journals and annuals and receives 40 journals free of charge. The present stock of bound journals is approximately 7000 and the books' stock is approximately 6000; many of the latter were purchased with funds provided by voluntary donors.

A regular Library Bulletin is issued listing recent papers published by members of the Agency staff and all books newly received in the Library.

The Librarian participates in the preparation of the *Directory of On-Going Research in Cancer Epidemiology.*

### (*b*) *Computerized bibliographic services* (Mrs M. Coudert)

The Agency's terminal now provides access to the files of the National Library of Medicine and Dialog, USA, as well as to Télésystème, France, and in particular Cancernet-CNRS, Villejuif, France, a highly specialized file on cancer which aims at providing only pertinent and not an exhaustive list of references.

During the past year, a total of 159 hours were spent to make 380 on-line searches and 48 off-line searches for staff members. A total of 24 monthly up-datings were provided to staff members.

## 3. COMMON LABORATORY SERVICES (Dr J. R. P. Cabral and Dr H. Yamasaki)

These include animal breeding, maintenance of the animal house, disposal of animal bedding and wastes, the histology laboratory and the glass-washing service. The Agency's scientists use animals bred in-house for the majority of their work, since they now have considerable detailed knowledge of the spontaneous tumour rates in the strains used—BDIV and BDVI rats and C57B1/6 mice.

The histology laboratory processes all the histological material from experimental animals in the Agency as well as biopsy material sent by Agency researchers doing field work abroad.

The glass-washing unit is a unified service for the experimental work carried out in chemistry, biochemistry and virology.

# EDUCATION AND TRAINING

## 1. RESEARCH TRAINING FELLOWSHIPS (Dr R. Montesano, Mrs M. Davis and Miss E. Welton)

Since its inception, this programme has been under the responsibility of Dr Walter Davis, who retired in October 1982; at that time Dr Ruggero Montesano was appointed Chairman of the Fellowhips Selection Committee.

### (*a*) *The Fellowships Selection Committee*

The Fellowships Selection Committee met in Lyon, 21–22 April 1983, to review applications; the members of the Committee were:

| | |
|---|---|
| Dr N. N. Blinov | N. N. Petrov Research Institute of Oncology, Leningrad, USSR |
| Dr R. Kroes | TNO Division of Nutrition and Food Research, Zeist, The Netherlands |
| Dr T. Kuroki | Department of Pathobiochemical Cell Research, University of Tokyo |
| Dr G. B. Mansourian | Office of Research Promotion and Development, WHO, Geneva, Switzerland |
| Dr T. J. Slaga | The University of Texas System Cancer Center, Smithville, Texas, USA (Representing the UICC) |

The Agency representatives were Dr Lenoir, Dr R. Montesano (Chairman) and Dr R. Saracci.

Before examining the applications received, the Fellowships Selection Committee discussed various items concerning the general policy of this programme. It was suggested that a review of the programme be undertaken after some 15 years of activity in order to ascertain its contribution to cancer research, with particular reference to training in epidemiology, fellowships awarded to candidates from developing countries, and complementarity with other fellowship programmes. The Fellowhips Selection Committee also discussed the criteria for the establishment of a Visiting Scientist Award for senior scientists, tenable at the Agency, to work on a collaborative research project.

### (*b*) *Fellowships awarded*

Out of 77 applications received, 20 were considered ineligible since their proposals fell outside the scope of the programme. The Committee recommended the awarding of fellowships to 16 of the 57 applications it reviewed; of these, five were for fellowships tenable at the Agency. The Visiting Scientist Award was made to Dr S. Preston-Martin, Department of Family and Preventive

Medicine, University of Southern California, Los Angeles, California, USA, who will work in collaboration with the Unit of Analytical Epidemiology on a project entitled 'A Case-Control Study of Childhood Brain Tumours in Europe'. The distribution by discipline of the fellowships awarded is given in Table 20, and the list of Fellows in Table 21.

Table 20. Distribution of research training fellowships by discipline, 1983

| Scientific discipline | No. of fellowships |
|---|---|
| Epidemiology and Biostatistics | 6 |
| Chemical Carcinogenesis | 3 |
| Viral Carcinogenesis | 1 |
| Cell Biology, Cell Differentiation and Cell Genetics | 3 |
| Biochemistry and Molecular Biology | 2 |
| Others | 1 |

Table 21. Fellowships awarded in 1983

| Name | Institute of origin | Host institute |
|---|---|---|
| BOSCH, F. X. | Servei d'Oncologia, Hospital Provincial, Girona, Spain | Unit of Analytical Epidemiology, IARC, Lyon, France |
| BUONAGURO, F. M. | Division of Viral Oncology, National Cancer Institute 'Fondazione Pascale', Naples, Italy | Tumor Biology Program, Fred Hutchinson Research Center, Seattle, WA, USA |
| CHIEN FANG | Department of Chemical Etiology & Carcinogenesis, Cancer Institute (Hospital), Chinese Academy of Medical Sciences, Beijing | Department of Biological and Medical Research, Argonne National Laboratory, Argonne, IL, USA |
| ENOMOTO, T. | Department of Physiology, Hiroshima University School of Dentistry, Hiroshima, Japan | Unit of Mechanisms of Carcinogenesis, IARC, Lyon, France |
| GUREVICIUS, R. | Cancer Control Department, Lithuanian Cancer Research Institute, Vilnius, Lithuanian SSR, USSR | Unit of Biostatistics, IARC, Lyon, France |
| ISLAM, S. S. | International Centre for Diarrhoeal Disease Research, Bangladesh, Dacca, Bangladesh | Department of Epidemiology, University of Alabama in Birmingham, School of Public Health, Birmingham, AL, USA |
| JAMES, M. R. | Medical Research Council Cell Mutation Unit, University of Sussex, Brighton, Sussex, UK | Institut de Recherches Scientifiques sur le Cancer, Villejuif, France |
| KIMURA, A. | Department of Biochemistry, Kyushu University 60, School of Medicine, Fukuoka, Japan | Gene Molecular Biology Unit E.R. C.N.R.S. 201 & S.C. I.N.S.E.R.M. 20, Institut Pasteur, Paris |
| MENEGOZ, F. | Registre du Cancer du Département de l'Isère, Grenoble, France | Department of Epidemiology, Fred Hutchinson Cancer Research Center, Division of Public Health Services, Seattle, WA, USA |
| NAIR, J. | Carcinogenesis Division, Cancer Research Institute, Tata Memorial Centre, Bombay, India | Unit of Environmental Carcinogens and Host Factors, IARC, Lyon, France |

| Name | Institute of origin | Host institute |
|---|---|---|
| NARA, N. | 1st Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo | Division of Biological Research, The Ontario Cancer Institute, Toronto, Ont., Canada |
| RESTREPO, M. | Instituto Nacional de Salud, Grupo de Sanidad del Ambiente, Bogotá | Department of Epidemiology, Harvard University School of Public Health, Boston, MA, USA |
| ROTHBLATT, J. A. | Department of Pathology, Albert Einstein College of Medicine, Bronx, N.Y., USA | European Molecular Biology Laboratory, Heidelberg, FRG |
| SAITO, I. | Department of Microbiology, University of Tokyo Faculty of Medicine, Tokyo | The Imperial Cancer Research Fund, London |
| SAITOH, N. | Central Health Institute, Japanese National Railways, Tokyo | MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK |
| UMBENHAUER, D. R. | Physiology Department, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA, USA | Unit of Mechanisms of Carcinogenesis, IARC, Lyon, France |

## 2. TRAINING COURSES (Dr W. Davis & Mrs C. Déchaux)

### (*a*) *Statistical Methods in Cancer Epidemiology, Lyon 19–23 July 1982*

This course, which was the second of its kind organized by the Agency, aroused—as on the first occasion—a great deal of interest, and more than a hundred applications were received for places in the course. Unfortunately, only 43 participants coming from 22 different countries could be accepted. The programme was prepared and coordinated by Dr N. E. Day, from the IARC Biostatistics Unit; the other members of the teaching faculty included: Professor N. E. Breslow (University of Washington, Seattle, WA, USA), Dr D. Hémon (Epidemiological and Statistical Research Unit, Inserm U.170, Villejuif, France), Mr J. Peto (ICRF Cancer Epidemiology and Clinical Trials Unit, University of Oxford, UK), Mr P. Smith (Tropical Epidemiology Unit, London School of Hygiene and Tropical Medicine, London), Professor D. Trichopoulos (Department of Hygiene and Epidemiology, University of Athens) and Drs J. Estève, R. Saracci and J. Wahrendorf, from the Agency.

### (*b*) *Epidemiological Aspects of Occupational Cancer, Kitakyushu, Japan 12–22 October 1982*

In collaboration with the University of Occupational and Environmental Health (President: Dr K. Tsuchiya) and with the support of the Regional Office for the Western Pacific, the Agency organized an international course on the epidemiological aspects of occupational cancer. The local organization was in the hands of Dr Takesumi Yoshimura, who dealt with all teaching facilities and domestic arrangements. The programme was coordinated by Dr Rodolfo Saracci from the IARC Analytical Epidemiology Unit. Other members of the faculty included Dr M. Gardner (MRC Environmental Epidemiology Unit, University of Southampton, UK), Professor T. Hirayama

(National Cancer Center Research Institute, Tokyo), Dr Geneviève Matanoski (The Johns Hopkins University, Baltimore, MD, USA), Dr A. H. Smith (Wellington Clinical School of Medicine, University of Otago, Wellington) and Drs L. Simonato and W. Davis, from the Agency. Dr K. Tsuchiya, Dr M. Kuratsune (University of Kyushu) and Dr W. Lloyd (formerly of the National Institute for Occupational Safety and Health, USA) contributed special lectures.

There were 27 participants from Japan and one from Thailand, one from Hong Kong and one from the People's Republic of China.

(c) *Workshop on Mutagenicity and Carcinogenicity Testing, Nairobi, 25 January–5 February 1983*

On behalf of the United Nations Environment Programme, the Agency organized a workshop on mutagenicity and carcinogenicity testing in Nairobi, at the beginning of this year, with the support of the University of Nairobi (Dr H. N. B. Gopalan), the International Association of Environmental Mutagen Societies (Professor T. Sugimura) and Associated Universities Inc. (Dr A. Hollaender). Dr Reuben Olembo (Director, Environmental Management Service, UNEP) provided guidance in the planning and made possible secretarial support. Dr Gopalan was responsible for local arrangements, and, especially, the preparation of the practical sessions, which were held in the Kenya Medical Research Institute (by courtesy of Dr S. N. Kinoti). The members of the teaching faculty included: Dr I. D. Adler (Institute of Genetics of the GSF, Neuherberg, FRG), Dr O. U. Alozie (UNEP), Professor E. A. Bababunmi (University of Ibadan), Dr R. J. Kavlock (US Environmental Protection Agency, Research Triangle Park, NC, USA), Dr B. K. Kilbey (Institute of Animal Genetics, University of Edinburgh, UK), Dr V. S. Turusov (All-Union Cancer Research Center, Laboratory of Chemical Carcinogenesis, Moscow), Dr P. Voytek (US Environmental Protection Agency, Washington DC) and Drs W. Davis and H. Yamasaki, from the Agency. There were 21 participants from four African countries (Kenya, Nigeria, Ghana and Uganda).

(d) *Epidemiology of Cancer, Karachi, Pakistan, 28 March–12 April 1983*

With the support of the Regional Office for the Eastern Mediterranean and the Jinnah Postgraduate Medical Centre, Karachi, the Agency organized a course on cancer epidemiology, similar to the one that was held there in 1977. The local arrangements were in the hands of Professor N. A. Jafarey. The programme was coordinated by Professor S. Grufferman (Duke University Medical Center, Durham, NC, USA); the other members of the faculty included: Dr F. Merletti (Institute of Pathology, Turin, Italy), Dr J. Osborn (Centre for Population Studies, London School of Hygiene and Tropical Medicine, London), Dr T. Yoshimura (University of Occupational and Environmental Health, Kitakyushu, Japan), Drs C. S. Muir and W. Davis, from the Agency, and Dr A. Modjtabai from the Regional Office. Specially invited lecturers from Karachi included Mr S. M. Ishaq, Drs N. A. Jafarey, S. N. Jafarey, S. H. Mansoor Zaidi and S. J. Zuberi.

Certificates were presented to the participants by Begum Afifa Mamdot, State Minister of Health, Special Education and Social Welfare.

There were 29 participants from four countries (Pakistan, Egypt, Cyprus and Sudan).

(e) *Statistical Methods in Cancer Epidemiology, Lyon, 27 June–1 July 1983*

The third in a series started in 1981, this course had the same success as the two previous ones: 47 participants coming from 18 different countries were accepted. The programme was coordi-

nated by Dr N. E. Day, from the IARC Biostatistics Unit; the other members of the faculty included: Professor N. E. Breslow (University of Washington, Seattle, WA, USA), Mr J. Peto (ICRF Cancer Epidemiology and Clinical Trials Unit, University of Oxford, UK), Mr P. Smith (Tropical Epidemiology Unit, London School of Hygiene and Tropical Medicine, London) and Drs J. Estève, R. Saracci and J. Wahrendorf, from the Agency. Dr (Mrs) S. Richardson, from the Epidemiological and Statistical Research Unit, INSERM U.170, Villejuif, France, had been invited but was unable to attend, for health reasons.

(*f*) *Future courses*

The courses on the epidemiology of cancer planned for 1983–1984 include:

— (in French), Yaoundé, 14–27 November 1983
— (in Spanish), Lima, 27 February–10 March 1984
— Rome, 19–31 March 1984
— Sydney, 20–31 August 1984
— Bangkok (date to be determined)

## 3. MEETINGS

*Nickel in the Human Environment, Lyon, 8–11 March 1983* [Dr W. Davis, Dr R. Saracci, Mrs M. Davis and Mrs C. Déchaux, in collaboration with the International Programme on Chemical Safety (Professor M. Mercier), the International Labour Office, Occupational Health and Safety Branch (Dr J. Sedlak), the Directorate-General for Science, Research and Development, Commission of the European Communities (Dr H. Ott and Dr A. Sors), the Health and Safety Directorate, Commission of the European Communities (Dr A. Berlin), and the French Ministry of the Environment (Mr A. Yana, Dr P. C. Jacquignon and Dr C. Rosenfeld]

Studies of the health hazards associated with exposure to nickel are concerned primarily with the cancer risk associated with its production, but there is growing interest in other toxic effects of exposure to nickel. This was reflected in the symposium held in the Agency's auditorium, which was attended by 150 participants from 23 countries.

Specially invited reviews were presented by 16 speakers; 23 proffered papers were also included in the programme.

The proceedings are being published in English by the Agency *(IARC Scientific Publications No. 53)* and in French by the National Institute for Health and Medical Research.

## 4. PUBLICATIONS (Mrs E. Heseltine, Mrs M. Coudert, Mrs J. Thévenoux, Miss E. Welton and Mrs M.-M. Courcier)

Dr W. Davis, who was responsible for the Agency's publications programme since its inception in 1971, retired in October 1982.

The Agency's editorial and publications service has expanded regularly, with 16 publications issued in the year 1982. The introduction of word processing equipment at the Agency has facilitated the work; and a number of books have been printed by electronic photocomposition from computer tapes made from word processor diskettes.

(*a*) *New titles*

Since the last *Annual Report*[1], 15 publications have appeared:

*Pathology of Tumours in Laboratory Animals*, Vol. III, *Tumours of the Hamster (IARC Scientific Publications No. 34)*

*Host Factors in Human Carcinogenesis (IARC Scientific Publications No. 39)*

N-*Nitroso Compounds: Occurrence and Biological Effects (IARC Scientific Publications No. 41)*

*Cancer Incidence in Five Continents. Vol. IV (IARC Scientific Publications No. 42)*

*Environmental Carcinogens. Selected Methods of Analysis*, Vol. 5, *Some Mycotoxins (IARC Scientific Publications No. 44)*

*Environmental Carcinogens. Selected Methods of Analysis*, Vol. 6, N-*Nitroso Compounds (IARC Scientific Publications No. 45)*

*Directory of On-going Research in Cancer Epidemiology 1982 (IARC Scientific Publications No. 46)*

*Cancer Incidence in Singapore (IARC Scientific Publications No. 47)*

*Cancer Incidence in the USSR (IARC Scientific Publications No. 48)*

*Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Polycyclic Aromatic Hydrocarbons (IARC Scientific Publications No. 49)*

*Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity No. 10* (non-serial publication)

*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 30, *Miscellaneous Pesticides*

*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 31, *Some Food Additives, Feed Additives and Naturally Occurring Substances*

*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 3, *Cross Index of Synonyms and Trade Names in Volumes 1 to 26*

*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 4, *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29)*

A full list of IARC publications is given on the inside back cover of this report.

(*b*) *Publications in preparation*

The following titles are being prepared for publication:

*Directory of On-going Research in Cancer Epidemiology 1983 (IARC Scientific Publications No. 50)*

*Modulators of Experimental Carcinogenesis (IARC Scientific Publications No. 51)*

*Second Cancer in Relation to Radiation Treatment for Cervical Cancer: Results of a Cancer Registry Collaboration (IARC Scientific Publications No. 52)*

*Nickel in the Human Environment (IARC Scientific Publications No. 53)*

[1] International Agency for Research on Cancer (1983) *Annual Report 1982*, Lyon, pp. 115–118.

*Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Hydrazines (IARC Scientific Publications No. 54)*

*Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Nitrosamides (IARC Scientific Publications No. 55)*

*Mechanisms, Models and Etiology of Tumour Promotion (IARC Scientific Publications No. 56)*

N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)*

*Environmental Carcinogens. Selected Methods of Analysis,* Vol. 7, *Some Metals*

*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Vol. 32, *Polynuclear Aromatic Compounds, Part 1, Chemical Environmental and Experimental Data*

*IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Vol. 33, *Polynuclear Aromatic Compounds, Part 2, Carbon Blacks, Mineral Oils and Some Nitroarene Compounds*

### (c) *Distribution and sales*

All IARC publications are distributed from WHO, Geneva. Up to the end of 1982, the numbers of copies of *IARC Scientific Publications* and of *IARC Monographs* that had been distributed and sold were as outlined in Table 22.

Table 22. Distribution and sales of IARC publications up to the end of 1982

| | Official distribution | Sales |
|---|---|---|
| *Scientific Publications* | | |
| No. 1 | 767 | 984 |
| 2 | 854 | 1491 |
| 3 | 1018 | 1066 |
| 4 | 979 | 1002 |
| 5 | 1113 | 1647 |
| 6 | 972 | 1416 |
| 7 | 1117 | 874 |
| 8 | 1105 | 1146 |
| 9 | 1055 | 954 |
| 10 | 1085 | 1080 |
| 11—Part 1 | 1143 | 682 |
| 11—Part 2 | 1147 | 696 |
| 12 | 1327 | 1248 |
| 13 | 1019 | 930 |
| 14 | 1021 | 911 |
| 15 | 1062 | 1109 |
| 16 | 1098 | 886 |
| 17 | 1043 | 536 |
| 18 | 1031 | 773 |
| 19 | 1170 | 679 |
| 20 | 964 | 530 |
| 21 | 1306 | 882 |
| 22 | 997 | 551 |
| 23 | 1096 | 969 |
| 24—Part 1 | 908 | 538 |
| 24—Part 2 | 910 | 537 |
| 25 | 1150 | 701 |
| 26 | 1085 | 510 |
| 27 | 1158 | 737 |
| 28 | 989 | 498 |

| | Official distribution | Sales |
|---|---|---|
| 29 | 983 | 659 |
| 30—Part 1 | 1187 | 657 |
| 30—Part 2 | 1187 | 640 |
| 31 | 1090 | 724 |
| 32 | 1864 | 2663 |
| 33 | 1360 | 1524 |
| 34 | 934 | 547 |
| 35 | 647 | 490 |
| 36 | 917 | 460 |
| 37 | 1752 | 566 |
| 38 | 921 | 546 |
| 39 | 1206 | 577 |
| 40 | 1376 | 146 |
| 41 | 1196 | 564 |
| 42 | 1240 | 628 |
| 43 | 1481 | 562 |
| 46 | 948 | 388 |
| 48 | 732 | 529 |
| *Non-serial publications* | | |
| Alcool et Cancer | 175 | |
| Cancer Morbidity and Causes of Death among Danish Brewery Workers | 462 | |
| Information Bulletin No. 8 | 348 | |
| Information Bulletin No. 9 | 342 | |
| *Monograph Series* | | |
| No. 1 | 2638 | 2099 |
| 2 | 2052 | 2410 |
| 3 | 2103 | 2388 |
| 4 | 1887 | 2280 |
| 5 | 2108 | 1962 |
| 6 | 1925 | 1973 |
| 7 | 2192 | 1748 |
| 8 | 2117 | 1750 |
| 9 | 2087 | 1595 |
| 10 | 2171 | 1770 |
| 11 | 2316 | 1451 |
| 12 | 2203 | 1608 |
| 13 | 2154 | 1442 |
| 14 | 2361 | 2078 |
| 15 | 2238 | 1600 |
| 16 | 2205 | 1524 |
| 17 | 3248 | 1412 |
| 18 | 2251 | 1441 |
| 19 | 2207 | 1398 |
| 20 | 2206 | 1290 |
| 21 | 2176 | 1077 |
| 22 | 2143 | 1174 |
| 23 | 2308 | 1183 |
| 24 | 2332 | 1084 |
| 25 | 2162 | 988 |
| 26 | 2239 | 846 |
| 27 | 2233 | 860 |
| 28 | 2268 | 836 |
| 29 | 2239 | 720 |
| Suppl. 1 | 2460 | 1450 |
| Suppl. 2 | 2489 | 1507 |
| Suppl. 3 | 2077 | 735 |

(*d*) *Scientific illustrations* (Mr J. Déchaux and Mr G. Mollon)

Illustrations for IARC publications, lectures, journal articles, poster presentations and other purposes are prepared by a draughtsman and a photographer. Photographic work is also carried out in connection with various laboratory activities.

## 5. SURVEYS OF RESEARCH WORK IN PROGRESS

(*a*) *Clearing-house for On-going Research in Cancer Epidemiology* (Dr C. S. Muir, Mrs A. Nagy-Tiborcz, Mrs E. Démaret and Dr D. M. Parkin; in collaborationwith Professor G. Wagner and Mr K. Schlaefer, German Cancer Research Centre, Heidelberg, FRG, DEB/74/003) (Supported by Contract No. N01-CO-55195 from the National Cancer Institute, USA)

The clearing-house for on-going research in cancer epidemiology was created in 1974 by the Agency and the German Cancer Research Centre, Heidelberg, Federal Republic of Germany and operates with partial support from the International Cancer Research Data Bank Program of the National Cancer Institute of the United States.

Seven annual directories have now been published. Although the content doubled between 1976 (622 projects) and 1982 (1275 projects), the Directory now seems to be tending to a 'steady-state', in that the number of projects initiated in 1982 more or less equalled the number completed or abandoned. In the first Directory, data were reported from 65 countries; in the 1982 issue this number had risen to 74. The 1983 Directory contains information on 1302 studies carried out in 80 countries.

The USA and the UK are still by far the largest contributors, followed by Japan, Canada and France. However, if the number of projects reported by a country is related to population size, the rank order is quite different, namely, Israel, Denmark, Sweden, UK and Canada (almost the same rank order being seen if number of projects is related to per-caput gross national product).

The most frequently studied cancer sites are lung, female breast, cervix uteri and liver, followed by stomach, leukaemia and childhood cancers. There has been no change in the distribution of sites under study since the inception of the clearing-house.

The clearing-house Directory provides a separate index of chemicals to facilitate identification of studies of human exposures. In 1983 this contained some 147 individual substances. An increasing interest in risk in defined occupational groups prompted the clearing-house to create an occupational index, which in 1983 listed 132 occupations under study. Emerging areas of interest in recent years have been, *inter alia,* protective effects of dietary items such as vitamins A and C, retinol-containing foods and fibre, and the relationship between psychological factors and cancer. Contrary to what might have been expected in view of the current emphasis on promotion in experimental carcinogenesis, few epidemiological studies were carried out on this topic.

The material in the clearing-house is used widely: it is incorporated not only in the CANCERPROJ and RPROJ data bases but also appears in the *Epidemiology Research Project Directory* and the *Toxicology Research Project Directory* published by the National Technical Information Service (USA) and in the *Selected Abstracts on Occupational Disease* published by the Department of Health and Social Security (UK).

(*b*) *Survey of Chemicals Being Tested for Carcinogenicity* (Mrs M.-J. Ghess and Mr J. Wilbourn)

The objective of this project is to survey on-going research on long-term carcinogenicity testing throughout the world. It was initiated in 1973 and is supported by the US National Cancer Institute. The major aims are to avoid unnecessary duplication of research, to increase communication between scientists and to make a census of available research facilities as well as of chemicals being tested. The collected data are collated, and synonyms, Chemical Abstracts Services Registry Numbers and use categories are added. The *Information Bulletins* are made available to participating laboratories and other interested scientists; they may also be purchased through the WHO Distribution and Sales Services.

The *Bulletins* list chemicals by investigation, use category, animal species, strain and number of animals in treated and control groups, route of exposure and dose levels tested, stage of experiment, and principal investigator(s). Survey results are arranged alphabetically by country, within each country by city and within each city by institute. For every institute that reports long-term experiments, the chemicals being tested (natural and synthetic, pure technical grades or product formulations, combinations and mixtures) are listed in alphabetical order. Advice on chemical nomenclature is given by Dr H. Bartsch (Unit of Environmental Carcinogenesis and Host Factors).

In February 1982, questionnaires were sent to already participating laboratories and to newly identified investigators. In addition, 92 institutes and pharmaceutical and industrial companies were contacted with a view to obtaining their participation in the survey; however, of the 14 replies received, only five provided information on long-term carcinogenicity testing.

*Information Bulletin* No. 10, which was published in December 1982, comprises data from 103 institutes in 16 countries on 1043 chemicals. Special attention was paid to ensuring that completed studies had been published and to verifying that studies already mentioned had not been discontinued. A total of 214 reports on 220 chemicals are listed.

Of the 1043 compounds undergoing long-term carcinogenicity testing, 182 (17.5%) have already been evaluated in the first 31 volumes of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. For fifteen of these chemicals, a positive association or a strong suspicion of an association with human cancer has already been established; and for 73 of the chemicals, there is *sufficient evidence* of carcinogenicity in experimental animals. For two of the compounds, the evaluations of *sufficient evidence* of carcinogenicity made in the *Monographs* were based on results of studies reported in this *Bulletin*. For the 861 chemicals that have not yet been evaluated within the *IARC Monographs* programme, the Survey provides a valuable guide for selecting those to be considered for future monographs.

Each *Bulletin* contains a section giving cross references to epidemiological studies listed in the IARC *Directory of On-Going Research in Cancer Epidemiology* in order to link the data on chemicals reported in the *Bulletin* with information on cancer risks in human populations possibly exposed to them. Of the 1247 projects in 64 countries listed in the 1982 Directory, about 210 are wholly or partly concerned with 51 of the chemicals or chemical substances listed in *Information Bulletin* No. 10.

In September 1983, an eleventh survey questionnaire will be sent to those laboratories that reported in *Bulletin* No. 10 asking for updated data on the chemicals listed. Efforts are also being made to contact other investigators who are carrying out long-term carcinogenecity testing but who are not reporting to the *Bulletin*. Any investigator not familiar with the *Bulletin* who would like to

receive a copy for information prior to submitting data on long-term tests underway is encouraged to contact the Unit of Carcinogen Identification and Evaluation, Division of Environmental Carcinogenesis, IARC.

## 6. VISITING SCIENTISTS

*Professor S. H. Chan* (Department of Microbiology, University of Singapore) visited the Unit of Biostatistics to prepare a paper summarizing the association between carcinoma of the nasopharynx and the HLA system. In addition, plans were developed to expand epidemiological studies in Singapore in the coming biennium.

*Dr B. P. Dunn* (Environmental Carcinogenesis Unit, British Columbia Cancer Research Centre, Vancouver, Canada) spent some days in the Unit of Environmental Carcinogens and Host Factors to familiarize himself with on-going nitrosamine research. He also visited the Unit of Mechanisms of Carcinogenesis to become acquainted with radioimmunological methods to detect DNA modified by carcinogenic agents.

*Dr L. Fishbein* (National Center for Toxicological Research, Jefferson, AR, USA) visited the Unit of Carcinogen Identification and Evaluation for a short period to assist with the activities of the Unit.

*Dr L. Griciute* (Oncological Institute of the Ministry of Health of Lithuanian SSR, Vilnius, Lithuanian SSR, USSR) visited the Unit of Mechanisms of Carcinogenesis to work on collaborative projects.

*Dr T. Heinonen* (Institute of Occupational Health, Helsinki, Finland) spent one month in the Unit of Environmental Carcinogens and Host Factors working on a research project to measure xenobiotic metabolism and lipid peroxidation in isolated hepatocytes.

*Dr M. Hollstein* (University of California, Berkeley, CA, USA) visited the Unit of Carcinogen Identification and Evaluation for short periods to assist in organizing a meeting on mechanisms of chemical carcinogenesis.

*Dr P. Kalliokoski* (University of Kuopio, Kuopio, Finland) spent one month in the Unit of Carcinogen Identification and Evaluation to assist in the production of monographs on polynuclear aromatic compounds.

*Dr V. Koblakov* (All-Union Cancer Research Centre, Moscow), on an IARC Research Training Fellowship, is spending one year with the Unit of Environmental Carcinogens and Host Factors to study the effect of dietary compounds on tumour initiation/progression.

*Dr J. H. Koziorowska* (Cancer Institute, Warsaw) visited the laboratories of the Unit of Mechanisms of Carcinogenesis and of the Unit of Environmental Carcinogens and Host Factors to update her knowledge in tissue culture techniques.

*Dr R. H. Laib* (University of Mainz, FRG) spent one week in the Unit of Environmental Carcinogens and Host Factors to conduct experiments on vinyl chloride-DNA adducts.

*Dr M. Lang* (EF-Lab, Helsinki and Department of Pharmacology and Toxicology, University of Kuopio, Finland) visited the laboratories of the Unit of Environmental Carcinogens and Host Factors to discuss future collaborative research projects on immuno-enzymatic techniques in studies on DNA damage caused by chemical carcinogens.

*Miss F. Marcenac* (Institut National des Sciences Appliquées, Villeurbanne, France) spent one month in the Unit of Environmental Carcinogens and Host Factors to receive training in experimental research methods.

*Dr F. Merletti* (University of Torino, Italy) visited the Unit of Carcinogen Identification and Evaluation for short periods to work on a review of target organs of exposure to carcinogens.

*Mr A. C. Povey* (Chelsea College, London University) is working in the Unit of Environmental Carcinogens and Host Factors laboratories on a microcapsule project in preparing his PhD thesis.

*Dr B. Singer* (University of California, Berkeley, CA, USA) visited the Unit of Environmental Carcinogens and Host Factors to discuss the planning of a meeting on cyclic carcinogen-nucleic acid base adducts to be held in September 1984 at the Agency.

*Dr A. Tzonou* (University of Athens) spent the year in the Unit of Biostatistics as an IARC Research Training Fellow. She has been involved in the analysis of case-control studies, and, in particular, a study of large-bowel cancer conducted in Athens.

*Annex 1*

# PARTICIPATING STATES AND REPRESENTATIVES AT THE TWENTY-FOURTH SESSION OF THE IARC GOVERNING COUNCIL 28–29 April 1983

*Australia*

Dr B. P. KEAN *(Vice-Chairman)*
Assistant Director-General
International Health and Tuberculosis Branch
Australian Department of Health
Woden, A.C.T.

*Belgium*

Dr J. FRANÇOIS
Director-General
Ministry of Public Health and the Family
Brussels

*Canada*

Dr E. SOMERS
Director-General
Environmental Health Directorate
Department of National Health and Welfare
Ottawa

Dr R. SIMARD *(Rapporteur)*
Scientific Director
Montreal Cancer Institute
Montreal, P.Q.

*France*

Professor J. ROUX
Director-General of Health
Ministry of Health
Paris

Dr A. LELLOUCH
Technical Adviser to the Ministry of Social Affairs and National Solidarity
Directorate-General for Health
Sub-Directorate for Programmes and Medical Treatment
Paris

Professor P. LOUISOT
Faculty of Medicine South Lyon
Laboratory of General and Medical Biochemistry
INSERM Research Group U.189
Oullins

Miss M. A. MARTIN-SANE
Multilateral Coordinator General,
Directorate for Cultural, Scientific and Technical Relations,
Ministry of External Relations
Paris

Mrs M. STAKIC
Deputy Secretary
General Directorate for Cultural, Scientific and Technical Relations
Ministry of External Relations
Paris

*Federal Republic of Germany*

Mr H. VOIGTLANDER
Director
International Health Relations Section
Federal Ministry for Youth, Family Affairs and Health
Bonn

*Italy*

Professor R. VANNUGLI
Director
Office of International Relations
Ministry of Health
Rome

*Japan*

Dr E. NAKAMURA
Director-General
Statistics and Information Department
Ministry of Health and Welfare
Tokyo

Dr N. KOINUMA
Deputy Director
Division of International Affairs
Ministry of Health and Welfare
Tokyo

*The Netherlands*

Dr J. SPAANDER
Lately Director-General of the National Institute of Public Health
Bilthoven

Ir. A.P.M. BERSEE
Staff Bureau of International Health Affairs
Ministry of Welfare, Public Health and Cultural Affairs
Leidschendam

*Sweden*

Professor H. DANIELSSON
Secretary-General
Swedish Medical Research Council
Stockholm

Professor L. ENERBACK
Department of Pathology
University of Göteborg
Göteborg

*Union of Soviet Socialist Republics*

Professor N. N. BLOKHIN
President, Academy of Medical Sciences of the USSR
Director-General, Cancer Research Center
Moscow

Dr Y. I. PUCHKOV
Chief, Department of International Scientific Relations
Cancer Research Center
Moscow

Dr (Mrs) T. A. SHAMARO
Senior Medical Officer
External Relations Department
Ministry of Health of the USSR
Moscow

*United Kingdom*

Sir James LEARMONTH GOWANS
Medical Research Council
London

Dr R. J. WRIGHTON
Senior Medical Officer
Department of Health and Social Security
London

*United States of America*

Dr G. T. O'CONOR *(Chairman)*
Director
Office of International Affairs
National Cancer Institute
Department of Health and Human Services
Washington, DC

Mr N. A. BOYER
Director
Health and Narcotics Programs
Bureau of International Organization Affairs
US Department of State
Washington, DC

*World Health Organization*

Dr LU RUSHAN
Assistant Director-General

Dr I. S. GLASUNOV
Director, Division of Non-Communicable Diseases

Mr A. GROENENDIJK
Director, Division of Budget and Finance

Dr J. STJERNSWARD
Chief, Cancer Unit

Dr C.-H. VIGNES
Legal Council

*Observers*

Dr A. ENGLUND
Executive Director
International Union Against Cancer
Geneva
Switzerland

Dr N. E. GRAY
Incoming Chairman
Scientific Council

*Annex 2*

# MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS NINETEENTH SESSION, 11–13 JANUARY 1983

Dr N. GRAY *(Chairman)*
Director
Anti Cancer Council of Victoria
East Melbourne, Vic.
Australia

Professor A. GEORGII *(Vice-Chairman)*
Secretary-General, German Cancer Society
Director, Institute of Pathology
Medical School
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*Annex 3*

# RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS 1 July 1982–30 June 1983

**Collaborative Centres**

| | |
|---|---|
| DEB/74/003 | Institute for Documentation, Information and Statistics, German Cancer Research Centre, Heidelberg, Federal Republic of Germany<br>(Clearing-house for on-going research in cancer epidemiology) |
| DEB/81/019 | Regina Elena Institute for the Study and Therapy of Tumours, Rome<br>(Reference centre for the epidemiology of precancerous lesions and environmental carcinogens) |

**Cancer registries/Incidence studies**

| | |
|---|---|
| DEB/73/016 | International Association of Cancer Registries (Provision of a secretariat and other supporting services) |
| DEB/78/014 | School of Public Health, Free University of Brussels, Laboratory of Epidemiology and Social Medicine, Brussels<br>(Study of digestive-tract cancer in Belgium) |
| DEB/81/023 | Ministry of Health, Suva<br>(Establishment of a population-based cancer registry in the Fiji Islands) |
| DEB/81/027 | London School of Hygiene and Tropical Medicine, London<br>(Case-control study of cervical cancer patients registered in selected cancer registries and clinics in the United Kingdom, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/81/028 | Danish Cancer Registry, Copenhagen<br>(Case-control study of cervical cancer patients in Denmark, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/81/029 | Finnish Cancer Registry, Helsinki<br>(Case-control study of cervical cancer patients in Finland, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/81/030 | Department of Gynaecology, Norwegian Radium Hospital, Oslo<br>(Case-control study of cervical cancer patients in Norway, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |

| | |
|---|---|
| DEB/81/031 | Department of Gynaecology, Karolinska Hospital, Stockholm<br>(Case-control study of cervical cancer patients in Sweden, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/81/036 | Slovenian Cancer Registry, Institute of Oncology, Ljubljana, Yugoslavia<br>(Case-control study of cervical cancer patients in Slovenia, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/81/042 | Department of Urology, Erasmus University, Rotterdam, The Netherlands<br>(IARC/Dutch-Japanese case-control study of prostatic cancer) |
| DEB/82/003 | Unit of Epidemiology, National Cancer Institute of Canada, Toronto, Canada<br>(Case-control study of cervical cancer patients registered in selected cancer registries in Canada, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/82/004 | Department of Epidemiology, National Institute for the Study and Therapy of Tumours, Milan, Italy<br>(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy) |
| DEB/82/005 | Department of Gynaecology, University Women's Clinic, Gottingen, Federal Republic of Germany<br>(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy) |
| DEB/82/007 | Institute of Radiotherapy, Oncological Centre, Prague<br>(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy) |
| DEB/82/008 | Women's Clinic, University of Heidelberg, Heidelberg, Federal Republic of Germany<br>(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy) |
| DEB/82/009 | Department of Radiation, University Women's Clinic, Munich, Federal Republic of Germany<br>(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy) |
| DEB/82/011 | Ontario Cancer Treatment and Research Foundation, Toronto, Ontario, Canada<br>(Case-control study of cervical cancer patients registered by the Ontario Cancer Treatment and Research Foundation, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/82/012 | Department of Radiology, Clinic of Gynaecology, University of Vienna, Vienna<br>(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy) |
| DEB/82/013 | Unit of Epidemiology and Biostatistics, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada<br>(Case-control study of cervical cancer patients registered in Manitoba, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation) |
| DEB/82/014 | Department of Chest Diseases, Hacettepe University, Ankara<br>(Field survey to investigate mesothelioma in central Turkey) |
| DEB/83/003 | Icelandic Cancer Registry, Reykjavik<br>(Case-control study of cervical cancer patients registered in Iceland to assess the risk of developing second primary tumours in patients exposed to radiation) |

DEB/83/004 National Cancer Society of Norway, Oslo
(Case-control study of cervical cancer patients registered in Norway, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/83/008 Cancer Institute of Montreal, Canada
(Long-term carcinogenic hazards of chemotherapy treatment for cancer)

DEB/83/009 Cancer Registry, Central Institute for Cancer Research, Berlin-Buch
(Long-term carcinogenic hazards of chemotherapy treatment for cancer)

**Studies on cancers linked with herpesviruses**

DEB/71/007 Shirati Mission Hospital, Tarime District, Tanzania
(Study of the epidemiology of Burkitt's lymphoma in the North Mara District, Tanzania)

DEC/81/026 Laboratory for the Epidemiology and Immunovirology of Tumours, Alexis Carrel Faculty of Medecine, Lyon, France
(Characterization of Epstein-Barr virus macromolecules and study of their role in cell transformation)

DEC/82/015 Department of Pediatric Surgery, Mustapha University Hospital, Alger
(Characterization of Burkitt's lymphoma in Algeria)

DEB/82/018 Ross Institute, London School of Hygiene and Tropical Medicine, London
(Analysis of malaria and Burkitt's lymphoma data collected in the IARC sponsored projects in the West Nile District of Uganda and Mara Region of Tanzania)

**Studies on liver cancer**

DEB/79/021 Department of Social Medicine and Public Health of the University of Singapore, Singapore
(Cohort study on hepatitis B carriers and liver cancer)

DEB/81/011 Immunology Section, University of Philippines, Manila
(Case-control study of parents of patients with liver-cell cancer and of control patients)

DEB/83/002 University Department of Medicine, Singapore General Hospital, Singapore
(Monitoring of liver cancer trends before and after the introduction of hepatitis B vaccine)

**Studies on nutrition and on cancer of the gastrointestinal tract**

DEC/81/001 Cancer Institute, Chinese Academy of Medical Sciences, Beijing
(Study on the endogenous formation of *N*-nitroso compounds in high- and low-incidence areas for oesophageal cancer in the People's Republic of China)

DEC/81/004 Leatherhead Food Research Association, Leatherhead, UK
(Determination of total *N*-nitroso compounds in the gastric juice of patients with precancerous lesions)

DEC/83/006 Aikita University School of Medicine, Aikita, Japan
(Study on the endogenous formation of *N*-nitroso compounds and nutritional status of subjects in high- and low-incidence areas for stomach cancer in Japan)

DEB/81/012 Danish Cancer Registry, Copenhagen
(Preliminary study on capability of persons to recall past food patterns)

DEB/81/037 Bacterial Metabolism Research Laboratory, Public Health Laboratory Service, Salisbury, UK
(Analysis of faeces and urine samples from persons taking part in IARC coordinated international study of diet and faecal characteristics in relation to colo-rectal and other cancers)

DEB/81/038 Medical Research Council, London
(IARC coordinated international study of diet and faecal characteristics in relation to colo-rectal and other cancers)

DEB/81/039 Queensland Institute for Medical Research, Brisbane, Queensland, Australia
(International collaborative study of diet and faecal characteristics in relation to colo-rectal and other cancers)

DEB/81/040 Regina Elena Institute for the Study and Therapy of Tumours, Rome
(Case-control study of adenomatous polyps of large bowel)

DEB/81/041 Public Health Laboratory Service, Centre for Applied Microbiology and Research, Salisbury, UK
(Analysis of faeces and urine samples from a case-control study of adenomatous polyps of the large bowel in Rome)

DEB/81/043 CSIRO Division of Human Nutrition, Adelaide, Australia
(Case-control studies of large-bowel cancer in Southern European migrants in Australia)

DEB/82/010 Edouard Herriot Hospital, Lyon, France
(Nitroso compounds of gastric juice)

**Studies on various other cancer forms**

DEC/78/013 Department of Clinical Genetics, University Hospital of Lund, Lund, Sweden
(Study on the possibility of correlating the karyotypes of cancer cells to specific etiological factors)

DEB/81/017 Danish Cancer Registry, Copenhagen
(Evaluation of screening programmes for the detection of cervical cancer)

DEB/81/018 Icelandic Cancer Detection Clinic, Reykjavik
(Study on the evaluation of screening programmes for the detection of cervical cancer)

DEB/82/019 Icelandic Cancer Registry, Reykjavik
(Evaluation of familial factors by determining risk for cancers of the breast and other sites)

DEB/83/005 Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada
(International study of malignant melanoma)

**Studies on chemical carcinogenesis**

| | |
|---|---|
| DEC/78/002 | School of Pharmacy, Catholic University of Louvain, Brussels<br>(Creation of an IARC Reference Centre for the in-vivo monitoring of drug metabolizing enzymes) |
| DEC/79/006 | Institute of Medical Sciences, University of Tokyo, Tokyo<br>(Mutagenesis and neoplastic transformation *in vitro* of cultured cells by environmental chemicals) |
| DEC/79/010 | Cancer Research Centre, Academy of Medical Sciences of the USSR, Moscow<br>(Investigation on the development of cellular and biochemical markers of in-vitro transformation of epithelial cells in culture) |
| DEC/80/001 | Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan<br>(Investigation of mutagenicity testing in bacteria and yeast by environmental chemicals within an international network of carcinogenicity testing) |
| DEC/80/012 | Institute of Oncology, Medical Academy, Sofia<br>(Long-term carcinogenicity testing of environmental chemicals) |
| DEC/80/013 | Institute of Oncology, University of Genoa, Genoa, Italy<br>(Long-term carcinogenicity testing of environmental chemicals) |
| DEC/80/018 | Curie Institute, Biology Section, Faculty of Sciences, Orsay, France<br>(Synthesis of unlabelled and radio-labelled chemicals to be used in experimental studies) |
| DEC/81/002 | Cancer Institute, Chinese Academy of Medical Sciences, Beijing<br>(Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines) |
| DEC/81/003 | Institute for Cell Biology (Tumour Research), University of Essen, Federal Republic of Germany<br>(Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines) |
| DEC/81/008 | Institute of Experimental and Clinical Medicine, Tallin, Estonian SSR, USSR<br>(Studies on the mutagenic and carcinogenic activities of fly ashes originating from the combustion of shale oil) |
| DEC/81/009 | Oncological Institute of the Ministry of Health, Ministry of Health of Lithuanian SSR, Vilnius, Lithuanian SSR, USSR<br>(Long-term carcinogenicity testing of environmental chemicals) |
| DEC/81/020 | Icelandic Cancer Registry, Reykjavik<br>(Study on the role of intragastric formation of *N*-nitroso compounds) |
| DEC/81/024 | Institute of Oncology, Medical Academy, Sofia<br>(Investigation on the possible relationship between endemic nephropathy, cancer of the urinary tract and ochratoxin contamination of food) |
| DEC/81/025 | Karolinska Institute, Clinical Pharmacology Laboratory, Huddinge, Sweden<br>(Studies investigating the comparative capacity of tissues and/or cells of human and rodent origin to repair DNA modifications induced by environmental chemicals) |

| | |
|---|---|
| DEC/81/032 | Institute of Occupational Health, Helsinki<br>(Study on sister chromatid exchange rates as an indicator of cancer risk in chemical carcinogenesis) |
| DEC/81/033 | N. N. Petrov Research Institute, Leningrad, USSR<br>(Study of role of promoting factors in possible carcinogenic effect of 5-bromodeoxyuridine) |
| DEC/81/034 | Oncological Research Centre, Moscow<br>(Long-term carcinogenicity testing of environmental chemicals) |
| DEC/81/035 | National Institute of Hygiene, Budapest<br>(Long-term carcinogenicity testing of environmental chemicals) |
| DEC/82/001 | The Life Science Laboratory, Teeside Polytechnic, Cleveland, UK<br>(Study on carcinogenic effects in the offspring of male Swiss mice treated with MNU or ENU before mating) |
| DEC/82/006 | School of Pharmacy, Catholic University of Louvain, Brussels<br>(Study on the promoting activity of diazepam and related compounds) |
| DEC/82/016 | Laboratory of Biophysics and Radiobiology, Free University of Brussels, Rhode-Saint-Genese, Belgium<br>(Investigation of an in-vitro assay for measuring genetic changes in mammalian cells) |
| DEC/82/021 | Centre for Medical Research, University of Sussex, Brighton, UK<br>(Studies of an in-vitro assay for measuring genetic changes in human cells) |
| DEC/82/022 | Joint Mass Spectrometry Center, Claude Bernard University, Lyon, France<br>(Study on the development of methods of analysis of carcinogens by combined high-performance liquid chromatography-mass spectrometry) |
| DEC/83/001 | Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK<br>(Preparation and characterization of antibodies against DNA modifications induced by nitrosamines to be used for the determination of human exposure to that group of carcinogens) |
| DEC/83/002 | Institute of Oncology, Ljubljana, Yugoslavia<br>(Study on the role of carcinogenic agents in determining the metastatic potential of the induced tumour) |
| DEC/83/003 | Institute of Industrial and Environmental Health and Safety, University of Surrey, UK<br>(Studies on analgesic associated renal pelvic and ureteral urothelial hyperplasia and carcinoma) |
| DEC/83/004 | University of Kuopio, Kuopio, Finland<br>(Purification of cytochrome P-450-DMN demethylase and preparation of its antibody) |

*Annex 4*

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*Annex 5*

# MEETINGS AND WORKSHOPS ORGANIZED BY IARC 1982–1983

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| Review board meeting for Manuals on Environmental Carcinogens Selected Methods of Analysis (Synthetic Oestrogens) | Lyon, 5 July 1982 |
| IARC expert group on Surveillance of Environmental Aspects in Relation to Cancer in Humans | Lyon, 7–9 July 1982 |
| Short course on statistical methods in cancer epidemiology | Lyon, 19–23 July 1982 |
| Planning committee meeting for the organization of a symposium on Burkitt's lymphoma | Lyon, 20–21 July 1982 |
| Editorial board meeting for a monograph on the IARC's oesophageal cancer studies in Iran | Lyon, 3 September 1983 |
| Meeting of the International Association of Cancer Registries | Lyon, 6–8 September 1982 |
| Programme committee meeting on the 8th international symposium on *N*-nitroso compounds to be held in Banff, Canada, in September 1983 | Seattle, USA, 10 September 1982 |
| Review board for Manuals of Selected Methods of Analysis | Seattle, USA, 13 September 1982 |
| Collaborative study on destruction of polycyclic aromatic hydrocarbons | Lyon, 21 September 1982 |
| Planning committee meeting for the organization of the meeting on 'Cancer and Ageing' to be held in Leningrad in December 1983 | Lyon, 29 September 1982 |
| Meeting of the Scientific Council's Sub-Committee | Lyon, 30 September–1 October 1982 |
| Review of the Agency's on-going and proposed studies on nutrition and cancer | Lyon, 30 September–1 October 1982 |
| Working group meeting on larynx cancer study | Lyon, 7–8 October 1982 |
| International course on occupational cancer | Kitakyushu, Japan, 12–22 October 1982 |

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| Working group meeting on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Food Additives, Feed Additives, and Some Naturally Occurring Substances | Lyon, 19–26 October 1982 |
| Editorial board for Manuals on Selected Methods of Analysis | Lyon, 28–29 October 1982 |
| Meeting on the IARC MMMF Study | Lyon, 1 December 1982 |
| Programme committee meeting for the organization of a symposium on 'Nickel in the Human Environment' held in Lyon, 8–11 March 1983 | Luxembourg, 13–14 December 1982 |
| Scientific Council | Lyon, 11–13 January 1983 |
| Workshop on mutagenicity and carcinogenicity testing (in collaboration with UNEP) | Nairobi, 24 January–5 February 1983 |
| International study to evaluate the risks of radiation exposure in cervical cancer patients | Lyon, 25–26 January 1983 |
| IARC working group for the updating of Volume 3 of the *IARC Monographs:* Some Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds | Lyon, 1–8 February 1983 |
| Mid-term meeting for Manuals on Selected Methods of Analysis | Lyon, 10 February 1983 |
| Programme committee meeting for the 8th international symposium on *N*-nitroso compounds | Lyon, 15–16 February 1983 |
| International Symposium on Nickel in the Human Environment (in collaboration with CEC/IPCS/ILO/French Ministry of the Environment) | Lyon, 8–11 March 1983 |
| Programme committee meeting for a symposium on the role of cocarcinogens and promoters in human and experimental carcinogenesis (held in Budapest, 16–18 May 1983) | Lyon, 22 March 1983 |
| International course on cancer epidemiology | Karachi, Pakistan, 28 March–12 April 1983 |
| Working group on Mechanisms of Chemical Carcinogenesis | Lyon, 11–15 April 1983 |
| IARC Fellowships Selection Committee | Lyon, 21–22 April 1983 |
| Meeting on pancreatic cancer | Lyon, 25 April 1983 |
| Governing Council | Lyon, 28–29 April 1983 |
| International symposium on the role of cocarcinogens and promoters in human and experimental carcinogenesis (in collaboration with the Hungarian Cancer Society) | Budapest, 16–18 May 1983 |
| Working group on time relationships in occupational epidemiology | Lyon, 24 May 1983 |
| Planning meeting for the preparation of a monograph on statistical analysis of cohort studies | Lyon, 25–27 May 1983 |

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| IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Carbon Blacks, Mineral Oils and Some Nitropolycyclic Compounds | Lyon, 7–14 June 1983 |
| Planning meeting for a multinational study on the epidemiology of lymphoid neoplasia | Lyon, 9 June 1983 |
| Meeting on collaborative studies for the Manuals on Destruction and Disposal of Laboratory Wastes (Hydrazines) | Lyon, 16–17 June 1983 |
| Meeting on collaborative studies for the Manuals on Destruction and Disposal of Laboratory Wastes (Nitrosamides) | Lyon, 20–21 June 1983 |
| Planning meeting for the preparation of a monograph on statistical analysis of long-term carcinogenicity assays | Lyon, 23–24 June 1983 |
| Programme committee meeting for a workshop on the role of drinking water in human cancer | Lyon, 23 June 1983 |
| Short course on statistical methods in cancer epidemiology | Lyon, 27 June–1 July 1983 |
| Review board meeting for Manuals on Selected Methods of Analysis (Mineral Fibres) | London, 29 June 1983 |
| Working group on some aspects of epidemiological research on possible cancer risk from exposure to silica | Lyon, 30 June 1983 |

*Annex 6*

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# VISITING LECTURERS TO IARC
## July 1982 – June 1983

| | |
|---|---|
| Dr J. C. Barrett | The role of chemically induced mutagenic events in neoplastic development |
| Dr G. Belvedere | Non-microsomal activation of styrene to styrene oxide |
| Dr P. M. Blumberg | Phorbol ester receptors and mechanisms of action of phorbol esters |
| Dr F. X. Bosch | Report on the site visit to Swaziland of the IARC/UNEP Project on Fungal Contaminants and Human Health |
| Dr P. Boyle | Recent advances in descriptive epidemiology: the Cancer Atlas |
| Dr W. Cavenee | Definition of polymorphic loci associated with retinoblastoma |
| Dr V. Craddock | Repair and replication of *O*-methyl-guanine DNA in relation to susceptibility to cancer induction by *N*-nitroso-*N*-alkyl ureas |
| Dr C. R. Gillis | Cigarette smoking and lung cancer in the West of Scotland |
| Dr A. Goudeau | Hepatitis B and primary liver cancer: perspective of prevention |
| Dr H. Hellberg | Health for all in the year 2000 |
| Dr M. Hollstein | A new *Salmonella* tester strain with A-T base pair at the mutation sites |
| Dr J. R. Idle | The role of pharmacogenetics in cancer epidemiology |
| Dr N. Ito | Antioxidants — Modifying activities in tumorigenesis |
| Professor O. H. Iversen | Some critical remarks to the paradigm of the two-stage theory |
| Dr A. Kaplan | Bioenergetic modifications in transformed cells: defective mitochondria and modified lactate dehydrogenase |
| Dr T. Kitagawa | *In vivo–in vitro* hepatocarcinogenesis and promotion |
| Dr P. Kleihues | Mechanisms of organ-specific tumour induction in the upper gastrointestinal tract |
| Dr N. Kobayashi | The Childhood Cancer Registry |
| Dr T. Kuroki | Can the two-stage model of mouse skin carcinogenesis be extrapolated to human skin? |
| Dr M. Lang | Immuno-enzymatic techniques in studies of DNA damage caused by chemical carcinogens |

| | |
|---|---|
| Dr A. D. Lopez | Widening sex differentials in mortality |
| Dr J. W. Lown | Mechanisms of decomposition under physiological conditions and of reaction with DNA of *N*-nitroso compounds of significance in cancer chemotherapy and carcinogenesis |
| Dr S. H. Lu | Occurrence and formation of nitroso compounds in mouldy food collected in China |
| Dr G. A. T. Mahon | The mouse spot test |
| Dr C. Martin | Identification of the major benzidine/DNA adduct *in vivo* in rat liver |
| Dr F. de Matteis | Disturbance of liver porphyrin metabolism caused by drugs and environmental chemicals |
| Dr J. J. McCormick<br>Dr V. Maher | The role of DNA repair in mutagenesis and transformation of human fibroblasts |
| Dr B. Mechler | Molecular cloning of a neoplastic gene in *Drosophila* 1(2)GL-lethal(2) giant larva |
| Dr N. M. Mironov | Accessibility of DNA in nuclear matrix-bound chromatin to polycyclic aromatic hydrocarbons |
| Professor R. Monier | Génétique moléculaire et cancer |
| Dr J. R. Nixon | Preparation and release from microcapsules |
| Dr F. Perrella | Nuclear receptors for phorbol esters in mouse liver and epidermis |
| Dr H. A. Peters<br>Dr D. J. Cripps<br>Dr A. Goomen | Turkish porphyria |
| Dr R. Peto | Ways in which laboratory discoveries can lead to epidemiologically testable hypotheses |
| Professor G. C. Rabotti | Transformation et production virale des cellules humaines diploïdes infectées par le virus du sarcome de Rous |
| Dr J. M. Rice | Carcinogenesis studies in non-human primates: comparative effect of direct acting agents in adult, pregnant and fetal animals |
| Dr R. W. Ryder | A proposed nationwide controlled study of EBV vaccine to prevent primary hepatocellular carcinoma in the Gambia, West Africa |
| Dr R. Saffhill | Measurement of alkylthymines and their role as promutagenic lesions |
| Professor R. Schulte-Hermann | Tumour promotion in the liver: mechanisms and implications |
| Dr H. F. Stich | Usefulness of the micronucleus test on exfoliated cells in the identification of population groups at high risk for cancer |
| Dr S. R. Tannenbaum | Endogenous formation of nitrate and *N*-nitroso compounds |
| Dr R. White | DNA sequence polymorphism: oncogenes and Gardner's syndrome |

*Annex 8*

# INTERNAL TECHNICAL REPORTS 1982–1983

| *IARC Internal Technical Report No.* | |
|---|---|
| 82/004 | Cancer registration in Europe, co-ordination and role in cancer control |
| 83/001 | Approaches to classifying chemical carcinogens according to mechanism of action. Joint IARC/IPCS/CEC Working Group, Lyon, France (11–15 April 1983) |

*Annex 9*

# PAPERS PUBLISHED OR SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS


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